

Medical
Notes

The American Journal of Obstetrics and Gynecology

VOL. XVI

ST. LOUIS, JULY, 1928

No. 1

Original Communications

RADIOTHERAPY IN CARCINOMA OF THE OVARY

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ATTENTION has recently been directed to the varied experiences with irradiation of ovarian carcinoma. The rapid growth of ovarian carcinoma, the marked tendency to metastasis through the profusion of blood and lymph channels, the facility to spread to neighboring organs and the easy propagation by peritoneal implantation make surgical cures difficult. The value of radiotherapy either as a means of palliation of symptoms or of arrest of growth when it has been impossible to remove the entire lesion surgically, is difficult to assess independently, since operative procedures with variable responses have recently preceded irradiation in the majority of cases. In an attempt to gain a clearer judgment of the subject we have studied the results in cases of ovarian carcinoma treated by radiotherapy in the years 1920 to 1923, inclusive, at the Mayo Clinic, and have assembled comparative data in the literature.

CLASSIFICATION OF TUMORS OF THE OVARY

The frequency of occurrence of tumors of most varied types in the ovary has been the occasion of numerous histologic studies of the pathogenesis, but no entirely satisfactory classification covering both clinical and anatomic features of the tumors has been presented. Gebhardt has divided carcinomas of the ovary into two classes: genuine idiopathic which develop directly from the unchanged ovarian tissue; and cystic which either develop from benign ovarian cysts through carcinomatous transformation or start as carcinomatous cysts. Döderlein, discussing

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

Pfannenstiel's¹⁷ complete classification of ovarian neoplasms on the basis of origin, whether from parenchyma, germ cells, or stroma, emphasizes the impossibility of making an absolute diagnosis of malignancy on histopathologic observations alone, since many ovarian tumors which cannot be so classified are proved malignant by the subsequent clinical course. He presents the following grouping based on clinical observations and anatomic studies: (1) definitely benign tumors, including simple serous cystomas, cystic embryomas (dermoids), fibromas, pseudomucinous cystadenomas and solid adenomas; (2) definitely malignant tumors, including carcinomas, sarcomas, and endotheliomas; (3) relatively malignant tumors, including the papillary serous cystadenomas, pseudomyxomas and the solid embryomas or teratomas. On a descriptive basis, the pathologists of the Mayo Clinic report malignant tumors of the ovary as (1) adenocarcinoma, (2) solid carcinoma, or (3) papillary carcinomatous cystadenoma of either the intracystic or extracystic type. Since in discussing prognosis definite pathologic entities must be considered, in my review no operative case has been included unless a report of carcinoma was given by the pathologist. I have, however, included two nonoperative cases in which the probable diagnosis was substantiated by clinical features and history. In reports in which the diagnoses have not been checked by microscopic examination there is a probability that cases of relatively malignant types are included and alter the result.

It is necessary to differentiate clearly primary and secondary ovarian carcinomas. While metastatic ovarian carcinoma was believed, by early pathologists, to be rare, Bucher, in a series of necropsies, found that bilateral ovarian carcinoma, considered primary at previous operation, occasionally proved to be secondary, the original carcinoma usually lying in the stomach or lower in the gastrointestinal tract. Schlagenhauser assembled from the literature seventy-nine cases in which both ovaries were involved; in sixty-one the primary carcinoma occurred in the stomach, in ten in the intestine, in seven in the gall bladder, and in one in the suprarenal gland. The extent of metastasis to the ovary is likely to overshadow the primary growth. Careful palpation of stomach and intestinal tract at the time of operation is necessary to preclude the presence of a primary growth. On the other hand, when carcinoma is primary in the ovary, metastasis may occur throughout the body. Coexistence of independent gastric and ovarian carcinomas and of uterine and ovarian carcinomas has been established by the distinctive pathologic features of the tumors. Frankl in eleven cases of concomitant ovarian and uterine carcinoma established two as primary in the ovary, and three as primary in the uterus; in six instances he could find no relation between the carcinomas. Pfannenstiel¹⁶ has suggested that the ovarian carcinoma is usually primary when associated carcinoma involves nearby organs, whereas it is more likely metastasis if the other carcinoma lies in a distant organ. In general, one

inclines to the view that ovarian carcinoma, coexistent with carcinoma of another organ, is secondary.

In a number of series of cases of ovarian tumor malignancy was found in approximately 10 per cent. Sarcoma of the ovary has been reported in infancy and early childhood and reaches the peak of its incidence at about the second decade when embryonic teratoma is also relatively common. Carcinomas are reported from the second decade until late in life, the highest incidence being reached in the fifth and sixth decades. Ovarian tumors are often symptomless until far advanced; this is especially true of carcinomatous growths which early become bilateral. The symptoms which have been noted most frequently are abdominal distention (due to ascites), pain, and amenorrhea or other menstrual disturbances. Since it is impossible by clinical examination to distinguish malignant from benign or relatively malignant ovarian growths, immediate operation should follow the discovery of every ovarian tumor. Nonpapillary or glandular pseudomucinous cystadenoma is benign, about 98 per cent of the patients with this lesion remaining well after operation. In a few cases, however, true carcinoma develops following partial removal of the tumor. In relatively malignant conditions, such as papillary serous cystadenoma, there is a greater percentage of malignant recurrence. Glockner found recurrence in 11 per cent and Pfannenstiel in 23 per cent after four or five years. In all cases of papillary growths bilateral salpingo-oophorectomy with hysterectomy is the operation of choice. If the papillary growth has broken through the surface of the tumor, ascites is usually present, and, in about 13 per cent of the cases observed, implants on the peritoneum have occurred, giving a malignant aspect. However, metastasis by way of blood or lymph stream does not occur, nor does one find the cellular characteristics of carcinoma, such as anaplasia and infiltrating destructive growth, but only a marked proliferative tendency of the epithelium. It is a known fact, but unexplained, that occasionally in cases in which there have been residual papillary implants on the peritoneum, complete cure results with the disappearance of these implants without further treatment.

Carcinoma of the ovary is bilateral in the majority of cases at the time of operation. Even in advanced diseases exploration is justifiable and may be substituted for paracentesis, since the small incision is of little more significance than the puncture wound and the evacuation of fluid is more thorough. Decided temporary improvement often results; the opportunity for accurate diagnosis is afforded. From 30 to 45 per cent of cases will prove operable. Bilateral salpingo-oophorectomy and hysterectomy are advocated even in cases of unilateral involvement and in spite of the high primary mortality, since the remaining ovary and uterus are the sites of predilection in the event of recurrence. According to Glockner's survey, in 61.6 per cent of

the cases free from recurrence the uterus had been removed, whereas hysterectomy had been performed in only 36.3 per cent in which there was recurrence. The conservation of the remaining ovary to guard against distressing symptoms of the menopause is of questionable value in view of the gravity of the prognosis. Hofmeier reported full-term pregnancy with delivery of a normal child occurring after operation in two of eighteen cases of unilateral ovarian carcinoma, in which one tube and ovary only were removed. Rochet reports a similar case in which intensive postoperative irradiation was given while the remaining ovary was protected. A normal child was born one year later and the patient was free from recurrence when last seen, two years after operation. Such conservative measures must be used only in selected cases.

Döderlein recommends incision into the remaining ovary since it may occasionally present a normal exterior but shows evidence of disease on section. Polak has noted that the conserved ovarian tissue, if diseased, rarely fulfills the desired function and adds to the distress of ensuing vascular phenomena.

RESULTS OF OPERATION

The immediate mortality for panhysterectomy in cases of malignant tumor of the ovary is high: Döderlein reporting 15.7 per cent; Zweifel 13.3 per cent; Schäfer 17 per cent, and Winter 24 per cent. The extent of malignant growth at the time of operation is of paramount importance in the prognosis, and of less importance the type of tumor. The experience of various surgeons is briefly noted.

Fromme found recurrence in 43 per cent of cases of unilateral ovarian carcinoma, within from one and a half to three years. Hofmeier reported thirty cases in which operation had been performed for unilateral involvement, in fifteen of which death had occurred: in ten in the first year, in two in the third, in one in the fourth, and in one in the eighth year. In the remaining fifteen, five years had not elapsed since operation. Schäfer reports seventy cases of primary ovarian carcinoma in which operation was performed with a primary mortality of 17 per cent (twelve cases); in the remaining fifty-eight cases operation was described as complete in forty-one, residual malignant tissue being left in seventeen. In twenty-five there was unilateral involvement, and in eleven of these (44 per cent) the patient remained well for more than five years. Only twelve of the total number (17.14 per cent) remained well for more than five years, including only one patient with bilateral involvement. Panhysterectomy was performed in fifteen cases of unilateral carcinoma and in seven there has been no further trouble; extirpation of one adnexum was performed in nine and in three there has been no recurrence; in the one case in which both adnexa were removed there has been no recurrence. Döderlein considered continued cures after operation for bilateral involvement so few as to permit of individual listing. He mentioned two cases presented by Pfannenstiel, two by Fritsch, one by Tannen, and two by Freund. Glockner found 100 per cent recurrence in a group of ten such cases, and Hofmeier reported nine deaths within three years in a similar group of ten; in the remaining case operation had been performed only a year before.

Without differentiation of extent or type of growth, but with exclusion of all cases with metastasis, Glockner, after a five year period of observation, found 29

per cent continued cures in cases of ovarian carcinoma. In the first year 54.5 per cent of the recurrences appeared; in the second year 22.7 per cent; in the third year 9.1 per cent; in the fourth year the same percentage, and the seventh year 4.5 per cent. Pfannenstiel reported recurrence in 74 per cent after four years; Heinricius in 80 per cent. After another year the percentage of continued cures in this group fell to 14.6. Döderlein reported that ten of seventy-two patients operated on are alive; however, only six of these were operated on more than five years previously.

Codman reviewed forty-one cases operated on at the Massachusetts General Hospital during a period of twenty-five years. All but two of the patients had died; Both had a colloid type of carcinoma; one was living after nine years and the other after more than four. Of the thirty-nine who had died, 74 per cent had survived less than one year. Cameron found that the average length of life after operation in his patients was from five to six months. The most favorable result in this group was in a case in which the patient lived nine years after operation before inoperable recurrence developed. Schmitz found recurrence after complete surgical extirpation in 85 per cent of cases of papillary carcinoma and in 65 per cent of nonpapillary carcinoma. Norris and Vogt concluded that prognosis was less favorable in cases of primary malignant lesion of the ovary than in cases of malignant degeneration of ovarian cysts.

IRRADIATION OF OVARIAN CARCINOMA

Improvement in these statistics will be the result of (1) earlier diagnosis, which apparently may be realized only through periodic physical examinations, including thorough gynecologic examination, since the disease develops insidiously and is often without symptoms until it is far advanced, and (2) supplementary treatment which may prevent recurrence or arrest the development of residual growths.

Radiotherapy has been the most promising supplementary treatment as yet tested.

Orbaan in 1920 reported eleven cases of ovarian carcinoma in which radiotherapy had been used, in half of the cases with benefit. Permanent cure was effected in one case, and in two cases the patient was well for three years. In seven cases in which the disease was advanced, there was benefit; in three earlier cases, however, there was no benefit from treatment. Dreuschuck and Lovas reported marked success in the treatment of two cases of inoperable carcinoma with extensive metastasis; one patient was regarded as clinically cured and the second as definitely improved. They found that severe reactions and bad results followed irradiation in some cases. Norris and Vogt found postoperative irradiation with either roentgen rays or radium uniformly unsuccessful in the small series in which they employed it. Holmes and Dresser have noted that there was marked improvement in certain cases of generalized abdominal carcinomatosis under irradiation, but in all cases relief was only temporary. Phillips treated three cases of carcinoma of the ovary with irradiation; in one case in which exploratory operation had been followed by irradiation, all clinical symptoms disappeared completely during a period of one and a half years. The growth then recurred and proved fatal. In one case of generalized carcinomatosis of the abdominal cavity no benefit resulted from treatment, and in a third case treatment was prophylactic after complete extirpation and the patient remained in good health. Walthard reported two cases in which radiosensitive car-

cinomas of embryonal origin were observed. In one case the ovarian tumor had been extirpated, a radical operation and transverse resection of the sigmoid flexure having been performed. After eight months extensive recurrence in the peritoneum and through the pelvis and vagina was noted and treated with radium. Six and a half years after treatment the patient was well. In the second case, a patient, aged twenty-three, was treated with roentgen rays for a tumor which filled the abdomen and pelvis. After nine weeks the tumor was reduced to a small mass which was easily removed and the patient was free from recurrence three and a half years later. Codman reported five cases from private practice (diagnosis not checked microscopically) treated by irradiation, two with marked success. Strassman reported thirty-two cases in which operation for ovarian carcinoma was not followed by irradiation, and in all of which death occurred, whereas twenty patients treated postoperatively by irradiation were still alive; 5 per cent, however, had been treated less than six months before, ten less than two and a half years before, and only two more than five years before. Strassman considered irradiation important in direct proportion to the size of the tumor removed at operation. Keene, Pancoast, and Pendergrass have reported twenty-four proved cases of carcinoma of the ovary treated with roentgen rays. In all cases the primary growth was incompletely removed at operation, or definite recurrence had followed complete removal. They found it impossible to predict the effect of irradiation in any given case. In some of the most advanced cases, in which there were large abdominal and pelvic masses, the response had been remarkably good even to small doses; in others, less advanced, the condition had not been appreciably affected even by enormous doses. They advise removal of the primary growth when possible even in the presence of peritoneal transplants, since subsequent irradiation then offers a fair prospect of temporary relief of symptoms, particularly of pain and ascites. In several cases in which the growth was not completely removed or it recurred, Döderlein has been able to arrest the further growth of the tumor and even to cause its disappearance by irradiation. He believes that although the mode of action and degree of efficacy of irradiation are still uncertain, it is a sin of omission to neglect to use it after complete or incomplete operation for ovarian carcinoma.

REVIEW OF CASES

In my study I have attempted to correlate with the late results, the type of carcinoma, the extent of involvement at the time of operation, the nature of the operation and the mode of postoperative irradiation.

Of the fifty-nine cases, there were twenty-nine of unilateral and eighteen of bilateral carcinoma, eleven of abdominal carcinomatosis originating in an ovarian growth, and one of recurrent ovarian carcinoma.

Of the unilateral lesions, eight were solid carcinomas, eight intracystic and eight intracystic and extracystic papillary carcinomatous cystadenomas, two adenocarcinomas, and three carcinomas unclassified because of degenerative change. The growth was adherent to the sigmoid and ileum in eight cases, had involved the fallopian tube in four cases and the uterus in eight. Visible residual malignant tissue or implantations remained at the time of operation in seven cases. Unilateral salpingo-oophorectomy was performed in five cases, bilateral salpingo-oophorectomy in five, panhysterectomy in seventeen, and the uterus and one tube and ovary were removed in two.

Postoperative irradiation for three patients in this group was applied by means of vaginal packs of radium in doses of from 700 to 2100 milligram hours. Two of the three patients are alive five years after treatment; one had a solid carcinoma for which panhysterectomy was performed, the other intracystic carcinomatous cystadenoma for which bilateral salpingo-oophorectomy was performed. The third patient, who at operation was found to have a solid carcinoma attached to the sigmoid, died after five months with extensive carcinoma. In fourteen cases radium packs in the vagina were combined with roentgen rays produced at moderate voltage tension (135 peak kilovolts) and applied usually so as to cross-fire the abdomen through four anterior and posterior fields. In several cases, subsequent courses of roentgen rays were given with intervals of one or two months, either at the Mayo Clinic or elsewhere. Eight patients of this group are alive five years or longer after treatment. The lesions in the eight cases include three carcinomatous cystadenomas; one adenocarcinoma which invaded the tube and uterus; one multilocular carcinomatous cystadenoma with solid areas; three solid carcinomas, the first with peritoneal implants, the second, a highly malignant small-cell tumor with metastasis to the mesenteric lymph nodes and invading the ileum and cecum, the third accompanied by annular papillary carcinoma of the uterus. In three of the eight cases the malignant growth had not been completely removed at operation because of extensive invasion. Death has occurred in six cases, in two of solid carcinoma, in three of an unidentified type of carcinoma, and in one of intracystic and extracystic carcinomatous cystadenoma.

Treatment by roentgen rays at 200 kilovolt tension was combined with vaginal packs of radium in five cases of unilateral ovarian carcinoma, two of which were not traced beyond a period of three and a half years, respectively. In both of these cases the lesion was of a papillary type, and the patients were well when last heard from. In a third case in which it had been impossible to remove a widespread carcinomatous cystadenoma completely, recurrence did not develop until three years after irradiation; the patient died six months later. In the remaining two cases of this group, one of adenocarcinoma, the other of intracystic carcinomatous cystadenoma, the tumor was apparently completely removed, but death occurred in three months and eleven months, respectively. Repeated courses of moderate-voltage roentgen rays alone were used in seven cases, all of unilateral tumor of the carcinomatous cystadenomatous type, in one of which surgical removal was incomplete. Three of these patients are well; two have not been traced for more than one and two years, respectively, although from indirect reports the former was alive four years and three months after operation. In one case, in which there was no visible residual malignancy, recurrence appeared within one and a half years after total hysterectomy in spite of continued bimonthly courses of roentgen

rays. Death occurred three years after operation. The remaining patient of the group was free from recurrence for three years after one course of moderate-voltage roentgen rays. The recurrence was treated with high-voltage roentgen rays and radium with temporary improvement; however, death ensued within a few months. When symptoms of recurrence or of renewed activity of residual malignant tissue manifest after a period of latency, further intensive irradiation, in my experience, has seldom been effective. The most favorable responses to high-voltage roentgen rays under such circumstances were in two cases in which pain was relieved for one year. One of these cases would not have been included in this series except for treatment of recurrent growth in 1923. Left oophorectomy was performed in 1917 for unilateral intra cystic and extra cystic papillary carcinomatous cystadenoma, followed by treatment with moderate-voltage roentgen rays for a period of two years. Recurrence developed in 1923, exploration was performed, and the tumor was found inoperable. High-voltage roentgen-ray treatment over the pelvis relieved pain and stopped the vaginal discharge for one year, then the patient became steadily worse and no improvement followed subsequent treatment. Death by suicide because of intolerable pain occurred in 1926.

Of the thirty cases in which the lesion was unilateral, including the case just described, four have not been traced within the last year; thirteen (50 per cent) are without evidence of recurrence, four after more than four years, eight after five years, and one patient after six years. In another case inoperable recurrence developed six years after operation. Of the four patients who have not been traced within the last year two were well at the end of three-year and three-and-a-half-year periods. In twelve cases in which the data are available, the symptoms of recurrence or renewed activity of the residual growth appeared in from a few months to six years: in four within the first year, in two during the second, in four in the fourth, in one in the fifth, and in one in the sixth, the average interval before recurrence being two years and five months. The average duration of life after treatment in the same group was two years and nine months. The lesions involving one ovary in the cases in which death had not occurred included four solid carcinomas, two intra cystic and five intra cystic and extra cystic carcinomatous cystadenomas, one adenocarcinoma and one papillary carcinoma with solid areas. Panhysterectomy with removal of one tube and ovary was performed in seven of these cases, bilateral salpingo-oophorectomy in two, and bilateral salpingo-oophorectomy with resection of the ileum in one.

The lesions in eighteen cases of bilateral ovarian carcinoma include fourteen intra cystic and extra cystic carcinomatous papillary cystadenomas, two solid carcinomas and two adenocarcinomas. The malignant growth had invaded the ileum and sigmoid in two cases, the broad liga-

ment in one case and the uterus in two cases. Peritoneal implants were noted at operation in four cases, and in two others the removal of the growth was reported as incomplete. Panhysterectomy was performed in fourteen cases, and bilateral oophorectomy in four. Nine patients were treated with vaginal packs of radium and with roentgen rays at moderate-voltage tension. Two of these patients are alive, one four years, and the other six years after operation. Roentgen rays alone, usually in repeated courses and often with a combination of rays produced at a moderate and high-voltage tension, were used in six cases. Two patients of this group are alive, one five years and the other seven years after operation. Thus there is a total of four patients with bilateral carcinomatous involvement alive, one each at four, five, six, and seven years after operation. In every case the lesion was of the intracystic and extracystic carcinomatous papillary cystadenomatous type, and panhysterectomy was performed. As a rule, the immediate result of irradiation was favorable. Two patients in an advanced stage of the disease remained in excellent health for more than a year; one patient, who died one year after operation, was found at necropsy to be free from recurrence of carcinoma, death having resulted from profuse hemorrhage caused by a gradually enlarging rectovaginal fistula. Because of malignant invasion of the rectovaginal septum, radium needles had been inserted, and were probably a factor in the development of the fistula. In one case in this group the ovarian carcinoma had apparently developed during pregnancy. Massive intrauterine doses of radium given immediately after delivery of the child had checked symptoms for several months. When the patient was first seen at the Mayo Clinic one year later, the growth was widespread with peritoneal and omental implants and a necrotic sloughing mass at the surface. The left tube and ovary were removed and palliative irradiation given, but entirely without effect. The patient died six months later. The average duration of life after treatment for the thirteen patients of this group who have succumbed was one year and eight months: eight died within one year, two in the second year and four in the fourth.

Exploration was performed in nine of the eleven cases of advanced ovarian carcinoma and a specimen removed for pathologic examination. The growth in each case was found to involve the omentum, intestines, and parietal peritoneum. In one case metastasis to the liver was present. Exploration was omitted in two cases, the diagnosis being based on the history and clinical data. Treatment in this group was usually instituted at greatly reduced dosage, since the patients are usually cachectic and unable to tolerate intensive irradiation. In a few instances, treatment given largely as a placebo resulted in improvement in the patient's condition which permitted more intensive irradiation to be given later. One patient so treated survived for four years, and

was in excellent health until a few months before death. A second patient improved for two years; then operation was performed elsewhere, and she died soon afterward. Six patients died within six months after treatment which apparently was ineffectual; one patient lived eight months and for the first six months after treatment was relieved of ascites. One patient died eleven months later having had only slight relief of symptoms. Experience at the clinic with this type of disease has proved that only carefully graded treatment should be administered.

SUMMARY AND CONCLUSIONS

1. Of the fifty-nine patients with ovarian carcinoma treated by irradiation at the Mayo Clinic from January, 1920, to January, 1924, eighteen survived for from four to seven years, seventeen being alive at present. Four of the fifty-nine patients could not be traced beyond a three-year period.

2. Although this group is too small to use as a basis of percentages of continued cures, the number of patients alive between four and seven years after operation compares favorably with the number mentioned in available reports of the results of surgical procedures alone.

3. The advanced cases and those in which the growth was not removed completely at operation in the group of continued cures apparently indicates that irradiation has been a factor in the result. The longer average interval of freedom from recurrence obtained in the present series in comparison with the early recurrence noted in other series may perhaps be attributed to postoperative irradiation.

4. Considerable palliation may result even in far advanced cases from the judicious use of radium and roentgen rays.

5. Repeated moderate irradiation, or carefully graded doses for cachectic patients have given superior results, at the Mayo Clinic, to those of more intensive irradiation.

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REBELLIOUS CERVICITIS FROM CYSTS HIGH IN THE CANAL*

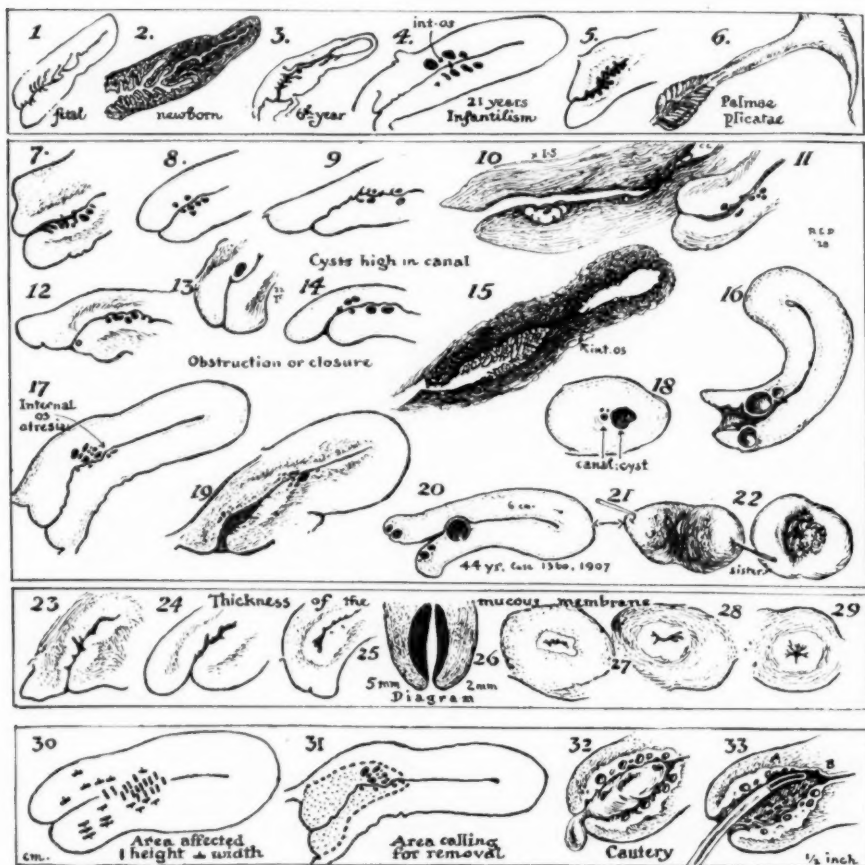
BY ROBERT LATOU DICKINSON, M.D., NEW YORK, N. Y.

(From the Committee on Maternal Health)

THE commonest pelvic disorder of women calls for new study, because of its important bearing on sterility and chronic leucorrhea. Gonorrhea, the one venereal disease now labeled in its obstinate form as "incurable," finds a favorite retreat in woman as an endocervicitis. One possible explanation of resistance to cure is a form of inaccessibility, the significance of which, as far as I know, has not heretofore been fully developed. This is a seat high up in the canal of the cervix. Attention was first drawn to the spot in the days when I developed a small cutting curette (from Delatours' fistula curette with a loop smaller than Craig's) to test and break up the thickened and cystic mucous membrane in the canal. Its importance was emphasized as one began in 1907 to follow canal infections farther and farther up with the electric cautery (Fig. 33). Even before this, high cysts were occasionally determined, in the times when one obtained good results in dysmenorrhea from regular office dilatation. In such a case, although the canal had been carefully wiped out and then iodine used, the dilator brought a gush of fluid which was thought to have been due to the bursting of a cyst or cysts well out of sight.

In a recent review of the literature showing many sections of the uterus I have noted a rather surprising frequency of cysts below, or at, or just above the internal orifice. In that much neglected art gallery called *Winckel's Pathologie der Weiblichen Sexualorgane*, at least a third of the uteri of active sex life show cysts high in the canal (Figs. 7, 8, 9, 12, 13, 14, 17). Hart's *Atlas* exhibits an atresia evidently due to a group of cysts (17). The Sellheim atlases yield the same surprises (4 and 18), and the Anatomy of Henle pictures as normal a section of the uterus (19) which shows cysts at and above the internal orifice of the cervical canal. Indeed, cysts above this level show in at least three of the sections here presented.

*Read before the New York Obstetrical Society, November 8, 1927.



LEGENDS FOR ILLUSTRATION

Rebellious Cervicitis (1) At forty weeks of fetal life, the long cervix shows deep folds in mucous membrane (Winckel). (2) A newborn uterus shows even deeper folds (Christeller). (3) These crypts may remain at sixth year (Christeller). (4) In a nullipara of twenty-one with infantilis, this full-length uterus exhibits cysts at and above external os (Sellheim, 1). See also 19. (5) Deep crypts in nullipara (Sellheim, 1903). (6) Symmetric palmar plicatae, cast of lining from nullipara of forty-two (Guyon). Figs. 7 to 22, Cysts high in canal, with none on vaginal surface except in 12, 20, 21, 22 (the only exceptions in twenty-five sections showing high cysts). Nos. 7, 8, 9, 12, 13, 14 are from Winckel; 11 from Christeller; 18 from Sellheim. The sound could not pass in many of these cases, as in 13, 17, 18 and 20; (10) Complete closure of internal os with cysts, in prolapse at sixty-nine, with chronic cervix catarrh (Christeller). (15) Senile cervicitis, retention cysts at seventy-five (Christeller). (16), (20), (21), (22) Diagrams from living uteri show cysts larger and more tense than sections from shrunken museum specimens (Dickinson). (17) Atresia at internal os from cysts in multipara (Hart.) (19) Cysts above internal os in anatomist's picture of normal uterus (Henle). (20) Section view of cysts exposed by tenaculum in 21, and in 22 similar condition in sister, both cured by caustery. Figs. 23 to 29, Evidence bearing on thickness of lining of canal to show depth of excision or caustery-roast required (drawn from Sellheim, 1900, and Winckel). Compare with 5, 7, 11, 12, 19. Five mm. is a frequent finding and 2 mm. next most common, 26. (30) Measurements from seventeen sections, showing distance of location of cysts above internal os and breadth of area affected. (31) The very large bulk or cylinder of tissue which operation would have to remove if all affected area were included, using 17 as an example. The vaginal cuff of a Sturmdorf operation would have to be very large. 32 Diseased area with narrow external os, and mucous distention of canal typical of this type of cystic trouble. (33) Nasal caustery, after dilatation, burns two strips. From A to B the cysts have been opened and radiated heat has sterilized at least 3 mm. beyond the contacts. The dotted line shows the next strip to be cauterized.

In looking over these sections attention should be paid to the marked thickness of the mucous membrane in the upper canal. This runs from 2 to 6 mm., 5 mm. being a not infrequent figure (26).

A further peculiarity of the chronically inflamed lining is the surface which gives through the curette a feeling of rough, tough gristle, as if the fingernail were scraped across the back of brussels carpet or linoleum. Such a surface is shown in Figs. 5 and 7, and is not merely due to *palmae plicatae*, as in 6.

These findings have an important bearing on the choice of curative treatment or operation. If amputation or coning is in question, it is to be observed that a very thick-tipped cone would be required to eradicate the diseased areas (Fig. 31). In some of the pictured sections such removal would involve bringing away something like a third of the bulk of the uterus, which would so maim the canal as to threaten its function and dilatability in labor.

Why not obliterate the offending cysts and infection instead of sacrificing structure? At least, if future childbearing is in question there is no excuse for such sacrifice, provided the hot platinum wire can properly open up and sterilize these areas. Such effective cautery action has been applied to a considerable number of these cases over a period of twenty years in the manner shown in Fig. 33. Beginning at the internal orifice, a gutter is burned through or nearly through the estimated thickness of the diseased lining and carried down toward the external orifice. A second groove is laid on the opposite side. If the canal is the size of the little finger, three lines are occasionally made in a first treatment, but I usually restrict myself to two because in a number of cases the extent of the radiation of the heat has reached a sufficient area. Three weeks later, in case mucopurulent secretion is still free or the sound finds rough areas in a relatively large canal, one or two lines are laid down on surfaces not previously attacked.

The most obstinate cases I have had, those requiring more than three cautery treatments, have been persistent infections of the upper part of the canal. Obviously, however, the clinical demonstration as to the level whence glairy mucus or mucopus makes its exit will only be demonstrable if one uses a tubular hysteroscope. This will be worth doing in obstinate cases, to search for cysts up the canal. An endoscope has a better field in the cervix than in the uterine cavity because there is less bleeding in this lower portion.

I am still watching for stenosis produced by the conservative, step-by-step procedure thus outlined, as part of ordinary office treatment. So far, no case needing subsequent dilatation has been detected in my series or that of Dr. Cary, even where relapse after months or years has called for repetition of cautery application.

NOTE: Since this paper was presented, A. H. Curtis has informed me verbally that he abandoned the use of radium within the cervix for the treatment of cervicitis early in 1925 or thereabouts, because of an occasional stricture and disturbance of menstruation even with small dosage. He has seen narrowing of the external os from the use of the cautery, but could not state whether this was due to the Post cautery. I ceased using the latter because the shank grows so hot as sometimes to cause a circular burn of the external os, where localized action up the canal is the only cauterization desired. Operators in San Francisco and Los Angeles have seen this burning at the os from the Post cautery, with need of dilatation later, as reported to me verbally in March, 1928. Cumberbatch, Corbus and others call for thirty to forty minute treatments once a week or oftener for weeks, which is to be contrasted with the few seconds of the cautery application. Hyams, after trying diathermy on thirty patients, reports that the sterilization action is not deep nor wide enough for effective work. The Filhos chemical cautery causes a cylindrical complete slough of the entire mucous membrane down to the musculature. Such action means closure of the canal in some instances. Therefore, if radium is found to reach too deeply and to affect the ovaries sometimes, and diathermy to act too slowly or superficially, we may again urge acquiring expertness with the simple hot wire.

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RELATION BETWEEN STRUCTURE AND PROGNOSIS IN CERVICAL CARCINOMA UNDER RADIATION TREATMENT*

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IT IS the purpose of this study to determine the relative value of histologic structure in the prognosis of cervical carcinoma, to observe the relation between histologic structure and response to radiation and to determine the extent to which the cell type may serve as a guide to treatment. The essential criteria for a study of this type are: (1) A sufficient number of cases to permit of accurate statistical deductions; (2) a group of cases which have been observed over a sufficient period to permit of judgment as to cure; (3) satisfactory biopsy material for histologic study and classification; (4) a uniform method of treatment applied to all cases; (5) a knowledge of the clinical extent of the disease at the time the treatment was begun, in order to evaluate properly this important factor in prognosis.

In our study all of these criteria are fulfilled. The material at our disposal consists of two hundred cases† of unmistakable carcinoma of the cervix treated in 1922 and 1923 whose present condition is known and from whom satisfactory tissue is available for microscopic study. Special emphasis is placed upon the fact that all the cases have been treated by radiation alone, the technic of which, with few exceptions, has been fairly uniform as to type and amount.

CLINICAL CLASSIFICATION

A classification of the cases into three clinical groups based upon the gross extent of the disease has been made, as follows:

1. *The Early Group.*—Composed of cases in which the disease is localized and confined to the cervix.

2. *The Borderline Group.*—Composed of cases in which the disease is more advanced, involving the paracervical tissues, or adjoining vaginal fornices, with slight fixation of the cervix, the uterus remaining freely movable and the parametrium uninvolved.

3. *The Advanced Group.*—Comprising those cases in which the disease has extended beyond the uterus and into the parametrium, resulting in more or less fixation of the uterus.

*Read at a meeting of the New York Obstetrical Society, December 13, 1927.

†The four-year cases have been included in order to make the analysis more accurate statistically by increasing the number of cases. The percentage of recurrences during the fifth year in patients who had been free of disease for four years is so small as to be negligible. The word *cure* is therefore qualified to mean freedom from disease four and five years.

TREATMENT*

The plan of treatment carried out has consisted in the application of radium in rather massive doses at the site of the primary lesion by means of buried emanation, vaginal applicators, and intracervical and uterine capsules. This has been combined with the use of x-rays. At the time the patients referred to in this paper were treated, low-voltage x-rays were employed. The circumference of the pelvis was divided into four quadrants, and one treatment was given to each quadrant, the tube being so placed as to be centered on the cervical lesion. This technic has been modified recently by the substitution of gold filtered seeds for the glass seeds and high-voltage x-rays for low voltage.

HISTOLOGIC CLASSIFICATION

The basis of classification which has been adopted is the *degree of anaplasia* of the tumor. The significant histologic signs of anaplasia are cellularity, variation in size and shape of nuclei, nuclear hyperchromatism, infiltrative tendencies, number and atypical quality of mitoses, loss of polarity, and absence of adult differentiated characters. A microscopic study of the biopsy material based upon these features demonstrated three fairly distinct groups. At one extreme there is a small group in which the tumor cells are highly differentiated, adult in character, with definite squamous tendencies, hornification and occasional pearl formation (Adult type, Grade I). At the other extreme there is a small though larger group in which the cells show complete loss of differentiation, absence of squamous characters, atypical qualities, and diffuse infiltrative growth with numerous atypical mitoses. The cells are small and round, or spindle in form, and the nucleus is markedly hyperchromatic (Anaplastic type, Grade III). Between these two extremes there is a larger intermediate group showing only partial differentiation and moderate anaplasia. In this group squamous characters are either slight or more often absent. The growth may be atypical, but lacks diffuse infiltration. There is a partial loss of polarity. These cells are large and frequently show a plexiform arrangement (Plexiform type, Grade II). This classification coincides in general with those of Schottlaender and Kermauner,³ Regaud, Martzloff⁴ and Broders.⁶

It is, of course, impossible to draw a sharp line of division between the three histologic groups. In a small proportion of cases it has been somewhat difficult to decide whether a tumor belonged to the plexiform or anaplastic group. Tumors presenting this structure, however, are distinctly radiosensitive and consequently are classified as anaplastic. The differentiation between the adult and anaplastic forms

*For a more detailed description of the treatment employed in these cases the reader is referred to references 1 and 19 in the bibliography.

has presented no difficulties and the presence or absence of squamous characters has served as a good basis for division between the adult and plexiform types. Table I shows the relative frequency of the different histologic grades as compared with Martzloff's⁴ classification.

As indicated in Table I, the majority of the tumors belong to the intermediate or plexiform group, whereas the smaller groups comprise the adult and anaplastic types of cell. Forty-two out of two hundred cases, or 21 per cent, belong to the highly undifferentiated anaplastic cell type. It is significant that one in five cases of this series is a very cellular, malignant and anaplastic tumor and consequently highly susceptible to radiation.

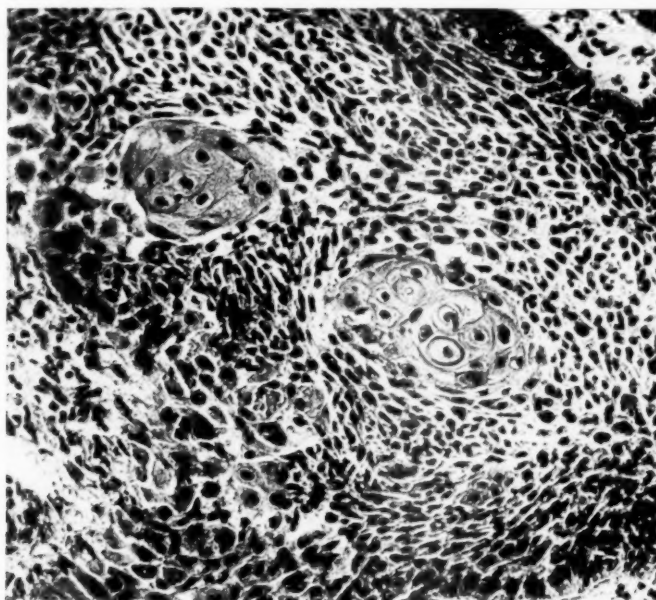


Fig. 1.—Photomicrograph showing epidermoid carcinoma of cervix. This is the adult, highly differentiated type with definite squamous characters (Grade I, radioresistant).

In order to study the relationship between histologic structure and prognosis, the distribution of the cell types among fifty cured cases is compared to their general distribution in the entire series, as shown in Table II.

TABLE I. SHOWING INCIDENCE OF STRUCTURAL TYPES AS COMPARED WITH MARTZLOFF'S THREE GROUPS

CELL TYPE WRITERS' CLASSIFICATION	NO. CASES	PER CENT	CELL TYPE MARTZLOFF'S CLASSIFICATION	NO. CASES	PER CENT
Adult (I)	35	17	Spinal	30	22
Plexiform (II)	123	62	Transitional	90	66
Anaplastic (III)	42	21	Spindle	17	12

TABLE II. SHOWING THE DISTRIBUTION OF STRUCTURAL TYPES IN FIFTY CURED CASES OF CARCINOMA OF CERVIX

CELL TYPE	NO. CASES	PER CENT	PERCENTAGE IN TOTAL SERIES
Adult	6	12	17
Plexiform	24	48	62
Anaplastic	20	40	21

It may be seen that there is a distinct increase of the anaplastic type of cell in the cured group over the percentage in the entire series (40 per cent as compared with 21 per cent). This would seem to

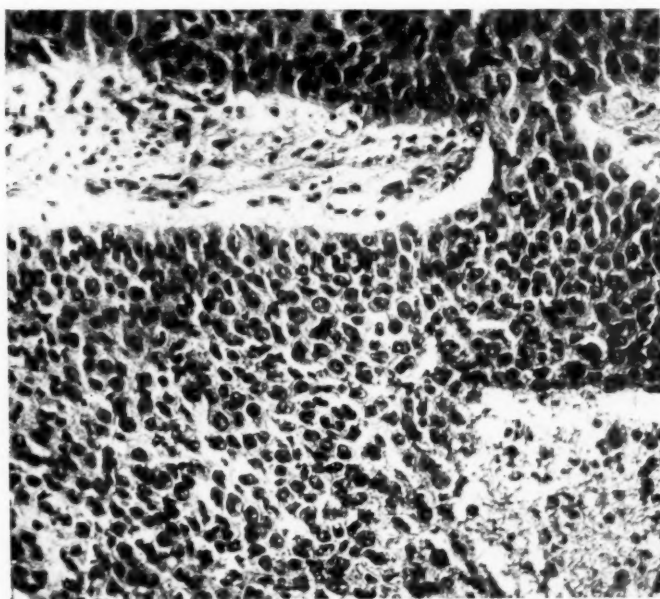


Fig. 2.—Photomicrograph showing plexiform epidermoid carcinoma of cervix. The structure is cellular and partly undifferentiated. Squamous characters are absent. (Grade II.)

indicate a decidedly better prognosis in the anaplastic type than in either of the other cell types.

There were twenty cases in which death occurred in spite of the early or borderline stage of the disease. In this group in which the clinical setting was favorable and the treatment similar to that generally employed, it seems logical to search for a cause for the unexpected result in the histologic structure. Table III shows the distribution of cell type in this group of cases.

Table III shows an incidence of 60 per cent in the intermediate or plexiform type, which is approximately the normal incidence of this type of cell. There is a slight decrease in the anaplastic type and increase in the adult type over the normal incidence. This comparison,

TABLE III. SHOWING DISTRIBUTION OF STRUCTURAL TYPES AMONG TWENTY FAILURES IN THE CLINICALLY EARLY AND BORDERLINE GROUPS

CELL TYPE	NO. CASES	PERCENTAGE IN 20 EARLY AND BORDERLINE FAILURES	PERCENTAGE IN TOTAL SERIES
Adult	5	25	17
Plexiform	12	60	62
Anaplastic	3	15	21

therefore, fails to show any definite relationship between the cell type and the result, and the deduction must be made that other factors which have not been recognized are responsible for these failures.

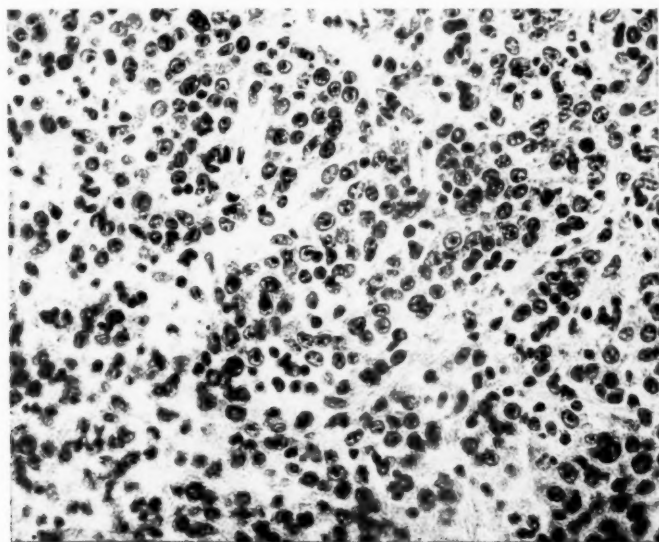


Fig. 3.—Highly cellular and anaplastic epidermoid carcinoma of cervix. The cells are small and atypical. There are numerous mitoses. The growth is diffuse and infiltrating. (Grade III, highly radiosensitive.)

TABLE IV. SHOWING DISTRIBUTION OF CELL TYPES AMONG 130 ADVANCED CASES WHICH FAILED TO SURVIVE

CELL TYPE	NO. CASES	PER CENT	PERCENTAGE IN TOTAL SERIES
Adult	24	18	17
Plexiform	87	67	62
Anaplastic	19	15	21

It is significant that only nineteen cases, or 15 per cent, belong to the anaplastic group as compared with an incidence of 21 per cent in the general group. The highly malignant type, therefore, fails to show a preponderance in this unfavorable group of cases; in fact the incidence is somewhat smaller.

A striking group of cases is that in which the disease was well advanced clinically, with fixation of the uterus and extensive para-

metrial involvement, yet in spite of these most unfavorable factors the patients were cured of the disease. Analysis of the treatment employed in this group of cases shows it to be essentially similar to that employed in the general group. It is of interest to note the distribution of cell type in this group, in order to determine whether the unexpected result may be explained on the basis of a special susceptibility to radiation. Table V shows the distribution of the three cell types in this group of cases.

It is interesting to note that in fourteen out of thirty cures of advanced carcinoma of the cervix, the histologic structure was of the

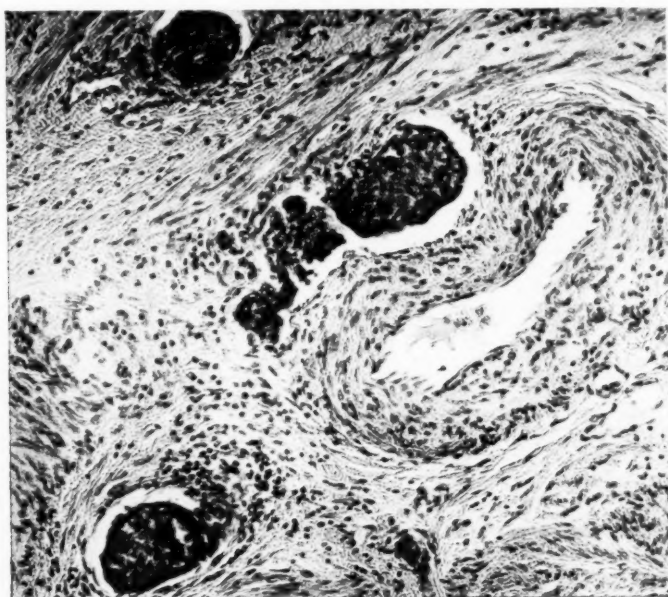


Fig. 4.—Very malignant and anaplastic carcinoma of cervix infiltrating wall of uterus and growing in perivascular lymphatics (Same case as Fig. 3.) The patient died soon after hysterectomy with widespread metastases.

TABLE V. SHOWING THE DISTRIBUTION OF STRUCTURAL TYPE AMONG 30 CASES OF ADVANCED CARCINOMA OF THE CERVIX WELL FOUR AND FIVE YEARS

CELL TYPE	NUMBER OF CASES
Adult	1
Plexiform	15
Anaplastic	14

most cellular and malignant type. This finding is of particular importance since it coincides with the theoretic principles involved and demonstrates the important fact that the radiosensitivity of the tumor expresses itself not only as a primary regression, but, with adequate radiation, as an ultimate cure in spite of the clinically advanced stage of the disease.

In order to further study the relationship between histologic structure and prognosis, the cases were divided into two groups, according to the clinical stage of the disease, as follows: (a) Early and borderline, and (b) advanced, and the percentage of cures in each group studied in relation to the histologic grade, as shown in Table VI.

TABLE VI. SHOWING PERCENTAGE OF CURES IN RELATION TO THE CLINICAL STAGE OF THE DISEASE AND THE HISTOLOGIC TYPE UNDER RADIATION AND SURGICAL TREATMENT, RESPECTIVELY

CELL TYPE	RADIATION				SURGERY	
	STAGE OF DISEASE	TOTAL NO. CASES	NO. WELL	PER CENT CURED	PER CENT OF OPERATIVE CURES, J.H.H. MARTZLOFF	PER CENT OF OPERATIVE CURES, MAYO CLINIC, BRODERS
Adult (Grade I)	Early and Borderline	10	5	50	47	53
	Advanced	25	1	4		
Plexiform (Grade II)	Early and Borderline	21	9	43	24	21
	Advanced	102	15	14		
Anaplastic (Grade III)	Early and Borderline	9	6	66	9½	9½
	Advanced	33	14	42		

Analysis of Table VI shows the relative effects of the clinical stage of the disease and the histologic cell type upon the prognosis. It is at once evident that the stage of the disease alone is a most important factor in prognosis. The cures effected in the early and borderline stage of the disease are comparatively high regardless of the cell type. The early and borderline cases have been grouped together in order to isolate the distinctly advanced cases as a test group. *The crucial test of the relative importance of the histologic type is to control the stage of the disease by studying prognosis in a group of advanced cases in which an unfavorable outcome is expected.* Results of the examination of the figures from this standpoint, comparing the percentage of cures in the three cell types of advanced cases, are shown in Table VII.

TABLE VII. SHOWING RELATION BETWEEN PROGNOSIS AND STRUCTURAL TYPE IN ADVANCED CASES OF CARCINOMA OF THE CERVIX TREATED BY RADIATION

CELL TYPE	NO. CASES	CASES WELL	PER CENT CURED
Adult	25	1	4
Plexiform (II)	102	15	14
Anaplastic (III)	33	14	42

It is quite evident from these figures that the prognosis in advanced cancer of the cervix under radiation therapy is extremely poor in the adult type and unexpectedly favorable in the anaplastic type. Only one case of the adult type out of twenty-five advanced cases, or 4 per cent, is cured as compared with 42 per cent cures in advanced carcinoma of the cervix of the anaplastic type. This result is especially

significant when it is considered that the total percentage of cures including early and borderline cases is only 25 per cent and the cures in the advanced cases in all histologic types 19 per cent.

The conclusion seems justified that in the advanced stage of the disease the prognosis improves with the degree of anaplasia when radiation is the therapeutic agent employed. The reason for this relation is obvious when the greater radiosensitivity of the more cellular and anaplastic tumor is taken into account.

The important rôle played by the stage of the disease in prognosis is well recognized. When the entire series of cases is divided into the three clinical groups defined above and compared with the results, Table VIII is obtained.

TABLE VIII. SHOWING THE EFFECT OF THE CLINICAL STAGE OF THE DISEASE UPON PROGNOSIS

CLINICAL STAGE	NO. CASES	DEAD	ALIVE	PER CENT CURED
Advanced	160	130	30	19
Borderline	21	15	6	29
Early	19	5	14	74

The result of this comparison indicates the prognostic importance of the clinical stage of the disease. On the other hand, it is significant that as many as 19 per cent of the advanced group are well, whereas the total percentage of cures for all groups and stages of the disease is only 25 per cent. It is important in this connection to recall that 21 per cent of the entire series belong to the radiosensitive group. These figures are strikingly close. It may be stated generally that one in five cases of carcinoma of the cervix is highly radiosensitive, and that one in five cases is curable by radiation in the advanced stage of the disease.

RELATION BETWEEN AGE AND PROGNOSIS

Table IX is designed to show the relationship between age and prognosis. The cases in each age group are further subdivided into the three clinical stages of the disease in order to control this factor in prognosis.

It may be seen from Table IX that all the patients under thirty years of age failed to survive. It cannot be inferred from this, however, that the grave prognosis in this small group of cases is due to the age factor alone. It should be noted that five of the six patients were in the advanced stage of the disease and the sixth was a borderline case. The histologic structure in this group showed Grade I in two cases and Grade II in four cases. The higher percentage of cures in the 30 to 40 age group may be accounted for by the accidental distribution of cases (14 of the thirty were early and borderline). In

TABLE IX. SHOWING RELATION BETWEEN AGE AND PROGNOSIS IN CARCINOMA OF THE CERVIX

AGE	NO. CASES	PER CENT	STAGE OF DISEASE	NO. OF CASES IN EACH CLINICAL GROUP	PER CENT CURED IN EACH CLINICAL GROUP	AVERAGE PER CENT CURED IN EACH AGE GROUP
20-30	6	3	Early	0	--	0
			Borderline	1	0	
			Advanced	5	0	
30-40	30	15	Early	7	86	47
			Borderline	7	57	
			Advanced	16	25	
40-50	73	36	Early	6	67	28
			Borderline	11	36	
			Advanced	56	21	
50-60	56	28	Early	6	66	23
			Borderline	6	33	
			Advanced	44	16	
60-70	34	17	Early	0	--	21
			Borderline	6	33	
			Advanced	28	18	
70-80	1	0.5	Early	0	--	0
			Borderline	1	0	
			Advanced	0	--	

the remainder of the age groups the percentage of cures is about equal. From this comparison it would seem that there is no definite relationship between age and prognosis with the possible exception of patients under thirty years of age. It is possible that in this group the prognosis is worse, although our data fails to demonstrate definitely this relation.

DISCUSSION

The problem of histologic prognosis dates back to Hansemann,⁷ who introduced the term *anaplasia*. He believed that a direct relationship existed between anaplasia and degree of malignancy. Ewing agrees with Hansemann in this belief and utilizes the histologic signs of anaplasia as an estimate of the degree of malignancy. Schottlaender and Kermauner were among the first to divide epidermoid carcinoma of the cervix into three histologic grades and applied to them the terms mature, half mature and immature. This division is based upon the degree of anaplasia of the tumor. Broders' classification of tumors is also based primarily upon the conception of cell differentiation. Martzloff's classification of cervical carcinoma into spinal, transitional, and spindle-cell types is based upon the same fundamental conception of loss of differentiation or anaplasia. In his classification the spinal cell is the most highly differentiated and the spindle the least differentiated, whereas the transitional cell occupies an intermediate position. Using this grouping Martzloff found that when surgery is employed the prognosis was best in the spinal cell and worst in the spindle-cell type. Pemberton,⁸ using Martzloff's classification, concludes that the order of malignancy of the different cell types progressing from least to worst is spinal, transitional and spindle, thus agreeing with Martzloff. Kimbrough and Norris⁹ conclude that the spindle-cell type appears to be the most malignant, but believes that the stage of the disease at which treatment is instituted is the greatest prognostic factor in carcinoma of the cervix and is more important than the histologic type. These authors find a similar prognosis in tumors of least and highest malignancy and attribute this result to

the balancing of the two factors, malignancy and radiosensitivity. Regaud¹⁰ recognizes three histologic types of epidermoid carcinoma of the cervix and regards them of some prognostic value, although the therapeutic measures are not varied according to cell type. Schmitz¹¹ and his associates have endeavored to utilize histologic factors in prognosis and treatment of carcinoma of the cervix. Wintz,¹² states that the differentiation between immature, half mature, and fully mature carcinoma, has not, in his opinion, offered any practical results for either prognosis or treatment, and Plaut¹⁴ concludes that there is no reliable basis for histologic prognosis in cervical carcinoma.

The advent of radiation as a therapeutic agent in the treatment of cervical carcinoma lends a special significance to histologic prognosis. It should be emphasized that in a study of relation between structure and prognosis the therapeutic agent employed is a factor of prime importance. The varying degrees of malignancy described by Broders and later by Martzloff are based upon studies in which surgery was the treatment employed. These results state essentially that the prognosis is best in the most differentiated and adult tumors and worst in the very cellular, undifferentiated and anaplastic tumors. When radiation is used instead of surgery we find that this relationship is completely altered by the fact that the more cellular and undifferentiated tumors are the more radiosensitive and consequently offer a better prognosis.

The close relationship between clinical course, susceptibility to radiation and histologic structure found in this study coincides with a similar relationship observed in tumors in other locations. A distinct clinical, pathologic, and radiologic entity is encountered in so-called transitional cell carcinoma of the base of the tongue, tonsil, and nasopharynx.¹⁶ The essential feature of this disease is the radiosensitivity of a group of anaplastic epithelial tumors found in these particular regions. Operative removal of the primary lesion, or metastatic nodes, results invariably in local recurrence and wide dissemination of the disease, whereas their response to radiation is phenomenal. An analogous situation is found in the operative removal of a highly cellular anaplastic carcinoma of the cervix. When rapid local recurrence and distant metastasis follow hysterectomy in an apparently favorable case, the cell type is usually of the anaplastic variety (Grade III), and consequently is especially amenable to radiation instead of surgery.

Although the results of surgery in the treatment of malignant disease are dependent upon numerous factors, it is a well recognized fact that the degree of malignancy of the tumor is one of the most important determining factors. The best results are obtained in the most adult and differentiated type, whereas the worst results occur in the surgical treatment of the very malignant cellular tumors. Thus Martzloff quotes the following statistics from the Mayo Clinic and the Johns Hopkins Hospital.

TABLE X. PERCENTAGE INCIDENCE OF FIVE-YEAR CURES FOR THE DIFFERENT TYPES OF EPIDERMOID CARCINOMA OF THE CERVIX UTERI

	SPINDLE-CELL CANCER GRADE II OF BRODERS	TRANSITIONAL CELL CANCER GRADE III OF BRODERS	SPINAL-CELL CANCER GRADE IV OF BRODERS
The Johns Hopkins Hospital (Martzloff) (surgery)	47%	24%	9%
The Mayo Clinic (Broders) (Surgery)	53%	21%	9%
Memorial Hospital (radiation)	50%	43%	42 66%

The striking feature of this table is the very low percentage of cures in the spindle-cell group (9½ per cent). This is the cell type which is highly radiosensitive and in which our radiation results indicate 42 per cent cures, including the very advanced cases.

Since the advent of radiation, the problem of histologic prognosis has become somewhat confused. This confusion is due largely to the failure to recognize the fundamental biologic law, that the most cellular and most malignant tumors are at the same time the most radiosensitive. This brings about an apparently paradoxical situation in which the most malignant tumors should offer the best prognosis when radiation is employed. In view of the fact that the most malignant tumors offer the worst prognosis with surgery and the best with radiation, a comparison of two series of cases in which the therapeutic agents have not been considered is misleading. Another matter of confusion has been the use of the term "malignancy" in relation to radiation. Because of their radiosensitivity, the question has been raised as to whether the cellular and anaplastic tumors are, therefore, not less malignant. If this attitude is adopted, the degree of malignancy of a tumor must vary according to the therapeutic agent employed. It seems to the authors more sound to regard the degree of malignancy of a tumor as an intrinsic biologic property of the tumor and independent of external influences. Surgery and radiation are external agents and may affect the clinical course of the disease and alter the prognosis, but the degree of malignancy as a potential factor remains unchanged. It might be well to adopt Ewing's distinction between potential malignancy and clinical malignancy. From this viewpoint the former is a constant factor, whereas the latter varies and depends upon the therapeutic method employed.

The results of this study indicate a direct relationship between degree of radiosensitivity and percentage of cures. The results coincide with the theoretic principle involved. The low degree of malignancy of the adult and highly differentiated type of tumor is accompanied by a good prognosis only when the disease is in its early stages. These cures are effected by the caustic effect of a large dose of radiation upon an early lesion, so that the limited disease is eradicated in spite of

its radioresistance. When, however, this type of growth becomes more advanced and involves the parametrium, its prognosis becomes grave because we have to combat, not only an advanced lesion, but also a radioresistant lesion (see Table VI, 4 per cent "cures").

Examination of the anaplastic group (Grade III) shows a distinctly higher percentage of cures than in the other two groups. The remarkable feature is the high percentage of cures in the advanced cases (42 per cent). This result is attributed to the marked radiosensitivity of the anaplastic type of growth. It would seem, therefore, that the high potential malignancy and advanced stage of the disease are both offset by their marked susceptibility to radiation resulting in a cure in a high percentage of cases. In the intermediate group the tumor is neither highly malignant nor particularly radiosensitive. The lower percentage of cures in this group may be readily explained by the high proportion of advanced cases (83 per cent).

The observations recorded here find support in the studies of other investigators. Thus Martzloff quotes fifteen advanced cases of carcinoma of the cervix in whom the prognosis seemed very poor clinically, but the patients lived for a long time, some under radium treatment. Ten of these cases belonged to the histologically malignant group, consequently they were susceptible to radiation. Plaut finds four cures among nine cases of spindle-cell carcinoma treated by radiation and points out the good prognosis in the most malignant cell type as evidence against the value of histologic prognosis. It is important, however, to recognize that the poor results obtained by Martzloff in this group and the good results of Plaut may be explained by the fact that surgery was the therapeutic agent employed in the former group and radiation in the latter. These are precisely the results to be expected in the treatment of the most malignant type of tumor by surgery and radiation, respectively.

Apparently the same property of instability of the tumor process which renders a tumor more malignant and causes it to grow rapidly and disseminate widely also renders it more susceptible to radiation. The rapidly growing tumors as a rule respond rapidly to radiation and vice versa. Consequently the prognosis must depend upon the biologic response of the tumor to the particular therapeutic agent employed.

From a practical standpoint it is of some importance to be able to predict by histologic study what response to radiation may be expected in any given case. The ability to recognize histologically a group of carcinomas of the cervix which are especially unsuitable for surgery and peculiarly amenable to radiation may help to eliminate many of the unfavorable surgical results and decidedly improve the percentage of surgical cures where this method is still employed. In

the advanced cases this information may serve as a useful guide to radiation therapy.

SUMMARY AND CONCLUSIONS

1. The degree of potential malignancy of a given case of carcinoma of the cervix may be determined with reasonable accuracy by a study of the histologic structure. This information may be of considerable value in prognosis and treatment.

2. Epidermoid carcinoma of the cervix may be classified histologically into three grades, based primarily upon the degree of anaplasia. These groups correspond closely to three degrees of potential malignancy as well as to three grades of radiosensitivity (low, medium, and high).

3. The adult type of carcinoma of the cervix (Grade I) is markedly resistant to radiation; the anaplastic type (Grade III) is highly radiosensitive; whereas the plexiform type (Grade II) occupies an intermediate position.

4. The factors which determine prognosis in carcinoma of the cervix, as in other diseases, are multiple and not single. The clinical stage of the disease at which treatment is instituted and the radiosensitivity of the tumor are believed to be the most important factors in prognosis when radiation is employed.

5. Twenty to twenty-five per cent of carcinomas of the cervix are histologically very cellular, malignant, and anaplastic tumors and consequently are highly susceptible to radiation.

6. Under radiation treatment the prognosis of cancer of the cervix improves with the degree of anaplasia of the tumor. This is due to the greater radiosensitivity of the more anaplastic tumors and results in a high percentage of cures in a group in which the surgical results have been especially unfavorable.

7. Radiation therapy of advanced uterine cancer may result in a cure in a relatively high proportion of cases when the tumor is of the radiosensitive type, whereas in the radioresistant type the prognosis is distinctly worse and only a palliative result can be expected.

8. The results of this study confirm the biologic relationship between anaplasia and radiosensitivity and demonstrate the ability to cure advanced disease of the most malignant type by radiation in a high proportion of cases.

In the study of the histologic material from the cases included in this report, the authors are greatly indebted to Dr. James Ewing for much valuable aid and many helpful suggestions.

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121 EAST 60TH STREET.

(For discussion, see page 125.)

MIXED TUMORS OF THE CERVIX UTERI, "SARCOMA BOTRYOIDES," WITH A REPORT OF TWO CASES

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THE occurrence of mixed tumors of the cervix is comparatively rare. They are mesodermal in origin and the connective tissue element is usually the most prominent; therefore some cases, very similar to the ones here reported, have been described as sarcomas. These tumors may occur at any age, but for convenience they are divided into two groups: those in children and those in adults. Unlike vaginal mixed tumors, which are most common in infancy, mixed tumors of the cervix are much more common in the late decades. Mixed tumors in the infant are nearly always fairly typical, appearing as polypoid masses resembling a bunch of grapes. Those in adult life are not so constant in appearance. They may be very similar to those just described and may arise from the vaginal surface of the cervix or from the canal, protruding through the cervix. Others are firm and more or less typical of a true sarcoma. Metastases of the latter type frequently have typical botryoid characteristics.

Mixed tumors of the uterus are found mainly in the cervix. Only eleven cases have been described arising from the fundus, excepting the lipomas (simple lipoma, lipomyoma, lipofibroma, or liposarcoma), which occur chiefly in the fundus. There are no statistics available giving the number of reported cases arising from the cervix. It is sometimes very difficult to determine the exact site of origin, and a mistake can easily be made, due to the fact that many occur in children, and it is not easy to make a satisfactory examination of a child's vagina. More have been reported as arising from the vagina than

those having their origin in the cervix. Of the former type, McFarland collected 102 cases.

The clinical picture varies considerably. In the infant the tumor is usually first noticed when it appears at the vulva, although a blood stained discharge may precede the discovery of the tumor. In the adult a foul, blood stained discharge, dyspareunia, or the discovery of a mass in the vagina usually causes them to consult a physician. They may have backache, a feeling of weight in the vagina, and a bearing down pain. Small grape-like bodies are frequently passed and may be confused with a hydatidiform mole. If in a child, the growth is usually thought to be a simple polyp, and excision is advised. It quickly recurs and its malignant nature is then suspected or microscopic study may reveal its true nature. If in an adult, more radical surgery is frequently done. Surgery, however, has done very little more than give temporary relief, because there are no permanent cures on record. This is a clinical fact, proving the extreme malignancy of these tumors. However, the histologic appearance of these tumors does not give the impression of malignancy in every case.

They grow by direct extension involving the bladder or parametrium, but rarely the rectum. Pain on urination follows if the tumor extends into the bladder or cystitis develops from bacterial invasion. The primary or recurrent tumor soon attains large size, and symptoms of urinary obstruction develop. There may be painful defecation due to pressure, rather than to rectal involvement. Metastases, however, may occur in the neighboring lymph and blood vessels and rarely, distant metastases develop.

Several theories have been advanced as to the origin of these tumors. Kolisko and Hauser (as mentioned by Lynch) believe that they arise from fetal rests in accord with Conheim's theory. Wilms (according to Frank) believes that there is a displaced embryonal germ cell pushed down ahead of the wolffian duct. Frank goes on to say that this indifferent germ cell must be a mesodermal cell in order to supply the myotome (striped muscle) and mesenchymal (cartilage, etc.) derivatives.

CASE 1.—A. P. was born September 26, 1924, as the fourth child of normal healthy parents. Delivery was normal in every respect. Oldest sister died from rheumatism and endocarditis. One sister and one brother are living and well. On July 9, 1926, the child was brought to the Lakeside Dispensary and referred to the hospital for removal of a papilloma of the cervix. A few weeks before admission the mother noticed a red mass projecting from the child's vagina. This was easily seen when the child was standing, but in other postures often disappeared. There was no noticeable bleeding or increase in size. In spite of a good appetite, the child had been losing weight, was drowsy in the daytime, and cried during the night. Except for measles and varicella, the past history was negative.

The child at twenty-one and one-half months weighed only 19½ pounds. Upon inspection a moderately firm mottled yellow and greyish red mass was found pro-

truding from the vagina, resembling a cluster of very small grapes. The whole mass was 25 mm. long and 16 by 14 mm. in diameter. It was covered by smooth epithelium, and composed of a stalk, to which were attached the grape-like bodies by short pedicles. Some of the grape-like masses were seemingly cystic and others solid, of variable size, not exceeding 5 mm. in diameter. The tip was firmer than the base, and the polypi there were small.

On introducing an applicator into the vagina, the child cried, and when the child cried the tumor receded into the vagina. Gentle pressure on the abdomen brought about reappearance of the tumor. We were unable to determine the point of attachment of the tumor at that time. The inguinal lymph nodes were enlarged bilaterally, averaging 3 mm. in diameter. To a less extent the glands of the neck and axilla were also enlarged.

On July 10, a polyp was removed for biopsy and the pathologic diagnosis of sarcoma was made. On July 14 the patient was anesthetized. Examination showed the point of attachment to be the cervix. A tonsil snare was placed around the



Fig. 1.—Actual size of the original tumor in Case 1 with a probe through the cervical canal.

tumor and upon the cervix as far as possible and the tumor excised. Examination of the tumor showed that practically the entire cervix had been removed, that it had been amputated 18 mm. above the external os. There was also a smooth surface of peritoneum 8 mm. in diameter on the posterior surface of the upper portion of the excised mass.

The polypoid tumor was, as previously described, attached at its base to the portio and the lower cervix, but no sharp borderline could be made out. One of the swollen inguinal lymph nodes was also removed.

Microscopic sections, made through the grape-like proliferations, showed the free surface covered with a normal squamous epithelium. The tumor tissue began immediately beneath the vaginal epithelium and showed in some regions a slight infiltration with leucocytes.

Spindle cells were predominant, although occasionally a few round cells could be found. The spindle cells differed markedly in different parts of the tumor. In some areas the arrangement of these cells was very dense, of the classical

type of sarcoma, but there were other areas with loose myxomatous tissue, poor in cells.

The whole tumor was very rich in blood vessels, especially in thin-walled capillaries, and in certain places where there were many extravasated red blood corpuscles. Other sections made through the tumor near its axis revealed fairly large bundles of fibrous tissue, infiltrated by the above mentioned spindle cells. A few well preserved cervical glands could be demonstrated. One section was taken from the cut surface, where the tumor was amputated in the region of the internal os. It could be demonstrated that the lining cylindric epithelium was well preserved, the mucosa having normal crypt-like glands and being less lymphoid in character than the uterine mucosa, and quite typical for the cervix. The surrounding layer of smooth muscle fibrils was normal in appearance. No trace of infiltrative invasion of the malignant tumor below could be seen.

Sections, stained by the van Gieson method, presented in some areas single and sometimes small bundles of elongated narrow spindle-shaped cells, staining dark yellow, with a rod-shaped nucleus. Although in some of them a slight longitudinal striation could be seen, it was not possible to find any real cross striation. They were apparently embryonic smooth muscle cells. These could be found anywhere, in the grape-like proliferations directly beneath the epithelium and they had no connection with the musculature of the amputated cervix. They were, however, more numerous near the tumor axis.

The excised lymph node showed slight endothelial hyperplasia, probably in consequence of the moderate infection which the tumor had undergone. No trace of any metastasis could be detected in the lymph node.

The child was seen repeatedly after she had gone home. There has been some irritating discharge at times, but that only lasted for a few days at a time.

On February 15, 1927, the child returned with a recurrence which had been first noticed about one week previously.

Examination showed a mass almost as large as the original growth and similar to it, however the individual grape-like polyps were larger than those of the primary tumor. The point of attachment was sessile in character, and located on the anterior vaginal wall, extending from the vault of the vagina to about two centimeters posterior to the urethral meatus.

No attempt at radical removal was made, but the growth proper was removed and radium seeds were implanted in the anterior vaginal wall and broad ligament regions, radiation amounting to 792 millicurie hours.

Two days following this procedure, the child developed a severe proctitis with numerous watery stools containing gross blood. The temperature varied from 37.5° C. to 41° C. and the diarrhea continued for a period of ten days. One month after the operation, rectal examination showed induration of the posterior vaginal wall. A radium tube was applied to the vagina, radiation amounting to 100 milligram hours. This was followed by no reaction.

Patient was discharged April 17, 1927, having gained from 23 to 30 pounds during the two months' stay in the hospital.

The pathologic picture was very similar to the first sections. Smooth muscle cells were present in slightly greater abundance.

Patient returned to Lakeside Hospital and died April 18, 1928. Only a partial autopsy was permitted. The tumor which filled the pelvis was removed. There was also a large hydronephrosis and hydroureters due to pressure at the lower end of the ureters. Patient apparently died of uremia.

As previously stated the clinical history of similar cases has proved these tumors to be malignant. However, histologic study does not

always reveal definite evidence of malignancy. That is well brought out in this case.

CASE 2.—M. L., a white woman, twenty-nine years of age, rather short and stout, came to the Lakeside Dispensary on April 24, 1922, complaining of vaginal bleeding. Her last normal menstrual period was January 24, just three months prior to her visit. During the entire three months there had been an occasional show of blood. She had slight lower abdominal pain for one year, nausea for three weeks and for twelve days she had passed small bodies, very similar to small white grapes, and blood-tinged fluid. For twenty-four hours before coming to the dispensary, she had bled freely. There was no severe pain at any time.

Physical examination showed nothing abnormal, except in the lower abdomen and pelvis. Bimanual examination revealed a rather large cervix, especially the anterior lip, with a soft mass protruding through the cervical canal. The fundus was rather irregular and enlarged up to within 4 or 5 cm. of the umbilicus. Speculum examination revealed a mass of grape-like, gelatinous nodules, apparently protruding through the external orifice. A pinkish watery discharge and an occasional streak of bright red blood was escaping through the mass.

A provisional diagnosis of hydatidiform mole was made, but after admission to the hospital more careful examination showed that most of these polypoid growths were derived from the portio and a diagnosis of sarcoma botryoides was made. This was confirmed by microscopic examination of one of these polyps.

The patient had been married thirteen months and this was her first pregnancy. She had had frequency of urination and occasional slight vaginal discharge for about a year.

On May 1, 1922, when the patient was examined under anesthesia, it was found that this polypoid mass arose from the anterior lip of the cervix, extending into the external os and also upon the anterior wall of the vagina. Bimanual examination revealed a uterus about the size of a 2 to 3 months' pregnancy with a mass about the size of a normal uterus, attached to its left side. At operation this mass proved to be the nonpregnant side of a bicornate uterus.

A Wertheim hysterectomy was done. No enlarged lymph nodes were palpated in the pelvis or in the abdomen. Both ureters were dissected down to the base of the bladder and as much of the anterior wall of the vagina as possible was removed.

On pathologic examination the specimen was found to consist of a bicornate uterus, with both tubes and ovaries attached. One cornu was greatly enlarged, measuring 7 by 6 by 2 cm. The other cornu was essentially smaller, measuring 5 by 2 by $\frac{1}{2}$ by 2 cm. (measurements of preserved specimen). The peritoneal surface of the tubes showed a few fibrous tags and considerable injection of the blood vessels, but both fimbriated ends were patent. The ovaries showed no change. On opening the uterus, the uterine canal was found to be present in both horns. The enlarged one contained a fetus 7 cm. long, showing slight maceration.

The cervix was greatly enlarged and its mucosa roughened and wrinkled. From the anterior lip of the portio a growth extended into the cervical canal for a small distance, measuring about 2 cm. in diameter. It was reddish brown papillomatous tissue consisting of small grape-like berries the size of currents and not showing much solid substance. It extended to the muscular layer of the cervix.

Microscopic sections showed normal squamous epithelium below which there was a loose areolar tissue with round and spindle cells and dark stained round and oval nuclei and a huge number of capillaries, and in certain places collections of extravasated red blood corpuscles. Through a considerable number of fields the tissue was quite cellular, individual cells adjoining one another. There were regions

in which prominent strands of long, rectangular cells under high magnification showed distinct longitudinal striation and also a faint cross striation. With van Gieson stain, these cells were yellow; they were apparently embryonic striped muscle cells.

Slides made from other regions of the tumor showed a loose myxomatous basal substance with large fields of hyaline cartilage, sometimes interlaced by the above mentioned muscle fibrils.



Fig. 2.—Photograph of preserved specimen with fetus in one horn of the uterus.
Case 2.

In places the surface epithelium was absent; in the base there was considerable granulation tissue rich in wandering cells. The whole tumor was very vascular and in a considerable part of it, leucocytes predominated.

The patient made an uneventful recovery, leaving the hospital 18 days after the operation.

On June 1, 1922, radium (1000 mg. hr.) was applied to the upper vagina. On September 9 it was repeated and simultaneously 1200 mg. hr. were applied externally

over the left and 1200 mg. hr. over the right inguinal regions as well as 1400 mg. hr. in the midline above the pubes, making a total of 3800 mg. hr. used on external application. On October 18, 1922, patient came to the dispensary, and stated that she had had no pain or discharge, and had gained 10 pounds since operation. Examination showed the vault to be perfectly healed. There was a small mass in the rectovaginal septum, which felt like indurated tissue.

On November 27, 1922, patient returned complaining of lower abdominal pain of three weeks' duration. The examination was recorded as being negative. She was told to return one month later, but she came back in eleven days, complaining of considerable pain in the lower abdomen and back. There had been frequent and painful micturition and nocturia for about ten days. For one week she had vomited about twice daily and had more or less continuous nausea. Examination showed the vaginal vault smooth; a large tumor, however, on each side of the lower abdomen, could be palpated through the abdominal wall, the larger mass being on the right side. They were very hard, irregular in outline, and tender to palpation. No definite record was made as to the size of these tumors.

This was the last time she was seen at Lakeside Hospital. Later the patient went to a different hospital for examination, and a large mass in the lower abdomen was found. X-ray showed no bony metastases. She left that hospital against advice and died on or about March 12, 1923.

We wish to express our appreciation and gratitude to Dr. Howard T. Karsner, Chief of the Pathological Department of the hospital and Dr. W. H. Weir, Chief of the Gynecological Department, under whose care these patients were treated in the hospital, for their aid and advice in the presentation of this article.

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LOUISVILLE CITY HOSPITAL.

INTERSTITIAL PREGNANCY

A REPORT OF AN UNDIAGNOSED CASE WITH FATAL RUPTURE

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INTERSTITIAL pregnancy is by far the rarest of the varieties of ectopic implantation of the ovum with the exception of ovarian pregnancy. A fairly large number of cases have been reported, however, in recent years. Wynne, in 1918, collected eighteen cases and reports the frequency of the lesion as 1.16 per cent of a series of 1547 cases of ectopic pregnancy.

The difficulty of diagnosis before rupture and the danger to life if the diagnosis is not made make the lesion worthy of study. In our own case we were unable to rule out a normal pregnancy and allowed the patient out of our immediate observation, which entailed a fatal delay when rupture occurred.

Mrs. E. V., aged twenty-three years, para i, entered The Lakeside Hospital on March 17, 1925, complaining of morning nausea and vomiting of one month's duration, and of bloody discharge for the past week. That morning she had vomited and fainted and was sent to The Lakeside Hospital from another hospital with a diagnosis of threatened abortion. The anamnesis revealed nothing of importance except an abortion at two months four years before. Physical examination was negative. There was no bleeding. The cervix was practically normal in consistency. There was a slightly softened uterus, symmetric, freely movable, enlarged to the size of a three months' pregnancy. No lateral tenderness or abnormal masses were present. W. B. C. count 9,000, Hg. 80. Blood pressure and urine normal. Temperature range from 37 to 38. Last menstrual period had been December 11, 1924, previous one November 6, 1924.

The patient remained in the hospital four days. There was no recurrence of bleeding. She had no abdominal pain and her slight febrile reaction having subsided she was discharged on the twenty-first of March.

On March twenty-sixth the patient was admitted through the accident ward with a pulse of 140 and of poor volume, and showing all the symptoms of acute occult hemorrhage. She had had a sudden sharp pain at 4:00 A.M., ten hours before admission and had gradually increasing weakness, faintness, and pallor. Her pulse was of very low volume and no donor was available. Her blood pressure continued to fall progressively and an intravenous saline infusion was given immediately.

On pelvic examination there was nothing palpable in the abdomen other than the enlarged uterus. Rupture of the uterus was suspected and although there seemed very little chance of saving the patient it was decided to operate.

A laparotomy was performed and the uterus was found to be enlarged. The musculature of the fundus was torn from a point in the uterine portion of the tube at the left cornu to a point slightly more than half the distance to the opposite cornu. The fetus was in the uterus. Part of the placenta had been extruded into the abdominal cavity. The uterus was bleeding freely from a jagged laceration

which was about three inches long. It was sutured rapidly and the abdomen closed immediately. The blood pressure continued to fall and death occurred about one hour later.

Examination of the uterus which was obtained at necropsy disclosed the left cornu and more than half of its superior surface had been literally shattered as if by an explosion and the remnant of the cornual portion of the tube, which was markedly dilated, had ruptured into the peritoneal cavity as well as into the uterus. (Fig. 1.) The floor of the cavity (*b*) extended medially approximately to the line (*e*) marking the axis of the uterus. The cavity (*b*) showed upon microscopic examination a typical decidual reaction with chorionic villi. Part of the floor or partition between the uterine cavity and fetal sac was composed of muscle showing a decidual reaction both on the side next the fetal sac and the uterine side. Chorionic villi were seen only on the side of the interstitial cavity. There were diffuse adhesions

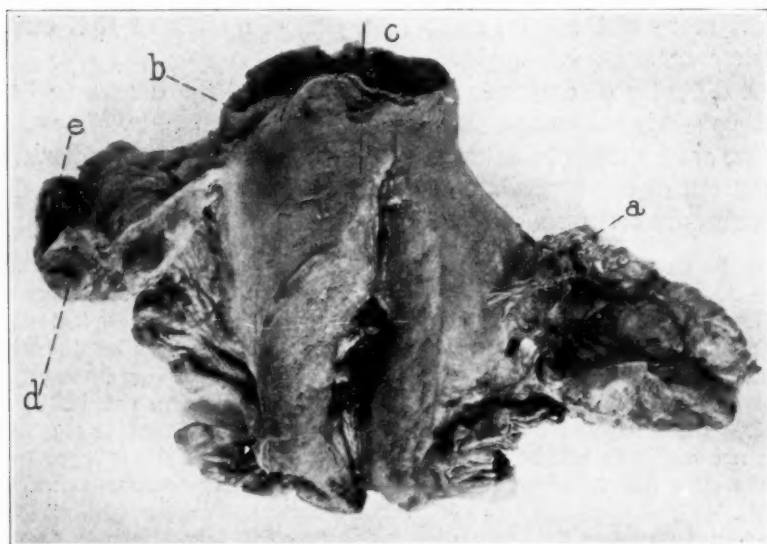


Fig. 1.—Posterior view of uterus and adnexa. (Autopsy) *a*, Omental adhesions; *b*, interstitial portion, left tube; *c*, axis of uterine canal; *d*, corpus luteum of pregnancy; *e*, adhesions.

on the posterior surface of the uterus involving both ovaries, and the convolutions of the tubes were bound together but the fimbriated ends of both tubes were patent. There was a typical corpus luteum of pregnancy in the left ovary.

It seems quite probable that the implantation in the present case was near the midpoint of the interstitial portion of the tube, inasmuch as rupture occurred both into the uterine cavity and externally. As pregnancy advanced, the muscular sac composing the cornua enlarged sufficiently to accommodate the pregnancy until it was of three months' duration. When the relatively thin musculature was unable to tolerate the strain, rupture occurred as it were centrifugally and centripetally, suggesting that implantation was neither at the tubal nor uterine end of the cornual part of the tube. Nidation at either extremity of the uterine portion of the tube commonly results in rupturing of the tube, tubal abortion or abortion into the uterus. "A shrapnel explosion," as in the present case, occurs usually in implantations of the ovum in the middle of the cornual portion of the tube.

The rupture of a cornual pregnancy may result in a rapidly fatal hemorrhage owing to the extreme vascularity of the pregnant myometrium, and the diagnosis is difficult in the absence of a typical ectopic history. Pain was not present in our case, and this was atypical in that the marked tension which is produced quickly usually causes pain in the expanding cornu as an early and prominent symptom before rupture or fetal death occur.

Uterine asymmetry (Ruge-Simon) in the form of elevation of the cornu on the pregnant side is often very difficult to appreciate at pelvic examination. If development upward takes place the uterus is elongated in the line of least resistance and the adnexa are higher on the affected

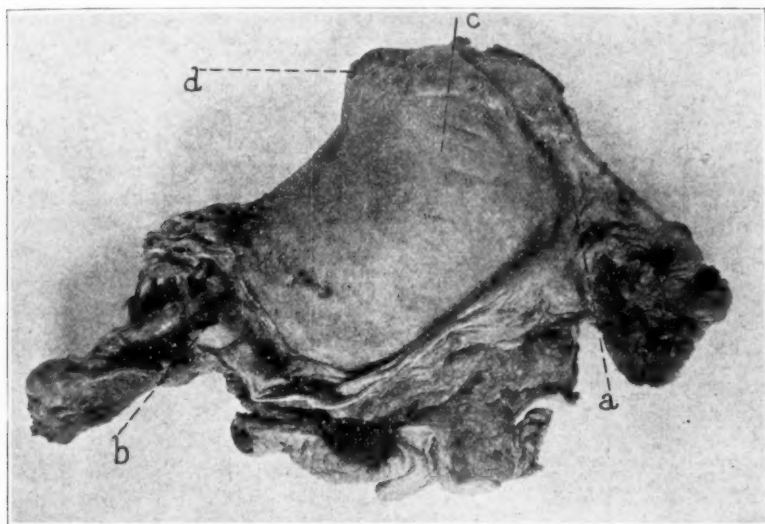


Fig. 2.—Anterior view of uterus and adnexa. (Autopsy) *a*, Insertion left round ligament; *b*, insertion right round ligament; *c*, axis of cervical and uterine canal; *d*, end of tear in uterine musculature.

side. (Fig. 2, *a*.) This does not follow necessarily if the development of the fetal sac is in a downward direction. The examination of the uterus in this case gave no evidence whatever of asymmetry on careful palpation and in the absence of pain a misdiagnosis seems excusable.

The fact that a patient may come so near the occurrence of a fatal catastrophe without any alarming symptoms whatever emphasizes the necessity for being constantly on the lookout for such a well-concealed disaster. The slightest bloody discharge during pregnancy should be regarded as a danger signal and not dismissed as presumably an innocuous discharge from the lower segment of the uterus not yet obliterated by the placenta and membranes.

1235 LAKESIDE AVENUE.

DIFFUSE PELVIC ENDOMETRIOMA CONSTRICTING THE URETERS

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THE case of pelvic endometrioma reported in this communication is of interest because the patient was observed clinically at intervals over a period of five years and a postmortem examination gave us the opportunity of studying the extensive lesions which were present.

The patient, a white married woman of thirty-two years, was referred to the clinic in 1922 with a diagnosis of malignancy of the uterus. The past history relevant to the condition reported begins with the onset of menstruation in the twelfth year. This recurred every twenty-eight days and was of four days' duration. The intermenstrual periods were normal. The amount of blood lost at any time was not unusual, although there was a moderate degree of pain. For three years the pain associated with menstruation had increased, and upon one occasion was associated with difficulty on urination. In addition to the symptoms directly referable to the pelvic organs, the patient had been constipated for two years prior to admission. There had been backache and a dull pain in the left leg for six years and for three years a similar pain in the right leg. These symptoms were more intense during menstruation.

Upon admission to the hospital, the general physical condition was negative. The abdomen upon inspection and palpation presented neither masses nor points of tenderness. Pelvic examination showed induration of the broad ligaments. The cervix was directed upward toward the symphysis, and the body of the uterus retroverted and fixed. Upon the right side of the vagina, beneath apparently normal mucosa, there was a small, indurated mass about 3 cm. in length and 1.5 cm. in width. There were two cystic structures 2 cm. in diameter, one posterior to the cervix, and the other in the posterior vaginal wall nearer the outlet. Upon rectal examination, a firm, irregularly nodular mass projected from the left side into the bowel and partly constricted its lumen. The mucosa covering the mass was not ulcerated. Although these pathologic findings suggested to the patient's physician the presence of a malignant growth of the pelvic organs, the preservation of weight, the general well-being, and the absence of ulceration of the palpable nodules was against this diagnosis. It was believed, rather, that the lesion was a diffuse adenomyoma, or was the result of endometrial implants. An exploratory laparotomy was advised, but the patient refused, and left the hospital without operative treatment.

Subsequently, she was seen at intervals of three to six months up to August, 1926. During this time, no marked changes were noted in the pelvic lesions. The pain during menstruation persisted, being sometimes extremely severe. In June, 1926, a bilateral oophorectomy was urged, but permission for the operation was refused.

In August, 1926, the patient was readmitted to the clinic. At this time, she complained chiefly of intermittent, cramp-like pains extending from the left iliac bone to the knee and occasionally to the foot. This attack came on during menstruation, and was so severe that the patient was hysterical, and morphia was neces-

sary for relief. Attempts to void had been associated with so intense pain there had been retention of urine for twelve hours. When catheterized, 750 c.c. of urine were obtained, and the patient was greatly relieved. The findings on vaginal examination were essentially the same as previously noted. Four days after admission the acute pain had subsided, and she was conscious only of discomfort in the left leg, which showed nothing abnormal beyond a limitation of hyperextension.

During an interval of two months, the patient was relatively comfortable, but in October, 1926, she was seen again at her home because of abdominal pain and difficulty in urination. The last menstrual period had ended three weeks previously, and had been associated with moderate discomfort. The October period had just begun. The day before admission, there was sharp pain involving the left costal margin, the left lumbar and sciatic regions, and the lower abdomen. This pain, in severity and diffuseness, exceeded the previous attacks and differed in that it involved the thigh. The bowels moved without difficulty. Except for pain over the renal region, there were no symptoms referable to the kidney.

Upon admission to the hospital, the blood pressure was 105/70, the temperature 101°, the pulse 100, and the respirations 22. A general physical examination revealed nothing worthy of note except the condition of the abdomen. The latter was symmetrical, but the lower quadrants were distended, and over these portions the note was tympanitic. The right kidney lay in the iliac fossa between the crest of the ilium and the costal margin. The organ was slightly enlarged, movable, and presented a firm, smooth surface. Palpation of the left upper quadrant revealed a soft, cystic tumor extending from the costal margin downward for a distance of about two inches. The tumor, which was slightly movable and tender on palpation, extended laterally to the crest of the ilium and medially to the midline.

Cystoscopic Examination (Dr. Deming)—The direction of the urethra was diagonally posterior, as seen in patients with cystocele. The bladder contained 200 c.c. of cloudy urine. Its capacity was 400 c.c. The base of the bladder was elongated, the trigone flat. No tumors, stones, or diverticula were present. The ureteral orifices were large and lay high up on the posterior wall. From the left ureter, thick pus escaped. A number six catheter could be passed for a distance of 12 cm., but it was impossible to pass a number four beyond this point. There was no evidence of function upon the right side, and a number four catheter could be inserted only 1 cm.

X-ray Examination.—X-rays and ureterograms were taken of the left kidney and ureter. The first 5 c.c. of sodium iodide solution showed the fluid collected in a dilated ureter. An additional 20 c.c. revealed a stricture near the intramural portion of the bladder, and a dilated, tortuous ureter, which, at the junction of the fourth and fifth lumbar vertebrae, formed an acute angle and followed a course laterally to the crest of the ilium.

Cultures of urine from the bladder and from the ureter were positive for *Staphylococcus aureus*. A diagnosis was made of pyoureter and pyonephrosis on the left side, and a temporary anuria upon the right.

Since the patient showed no improvement, it was decided to drain the left kidney. The operation was performed under local anesthesia. Upon opening the triangle of Petit, the kidney presented, and at the lower border was found a soft, cystic structure which was thought to be the ureter. Upon incising this structure, about 50 c.c. of purulent material flowed out. The lower pole of the kidney was then incised and the finger inserted through the incision into the renal pelvis which contained 500 c.c. of purulent fluid, positive for *bacillus coli*. A large rubber drainage tube was inserted through the lower pole into the kidney pelvis, and the wound was left open.

The patient stood the operation well, but her condition grew gradually worse, and she died eighteen days later. During this period, the nonprotein nitrogen of the blood increased from 87 mg. to 201 mg. upon the day of death.

Postmortem Examination.—The autopsy was limited to an examination through an abdominal incision. Upon opening the abdomen, the peritoneal surfaces were seen to be smooth and glistening, but 150 c.c. of a thin, sanguino-opaque fluid was found in the pelvic culdesac. Innumerable adhesions were present between the coils of intestines, being particularly dense over the large fluctuating mass of the right kidney. The pelvic tissues were densely adherent and formed one solid mass, extending laterally to the innominate bone and coalescing with it through an exostosis.



Fig. 1.—Uterus, bladder, ureters and kidneys removed en masse. Ureters dilated above stricture. Enlarged right kidney with dilated pelvis. Left kidney shrunken following incision and drainage.

Posteriorly, the mass encroached upon and constricted the rectum. The bladder was distended to a point 5 cm. above the symphysis, and the mucosa was congested. The body of the uterus, lying below the bladder, was pulled backward and to the left by adhesions. The cervix was so rigidly fixed in the mass of adhesions that it could not be satisfactorily palpated. The tubes and ovaries presented no gross abnormalities. Scattered over the pelvic peritoneum were tiny brown granular masses. Two small blood clots were attached to the anterior surface of the broad ligament. The kidneys, ureters, and the entire pelvic contents were removed en masse, (Fig. 1.) The right kidney was large, pale, and soft. It measured 14 by 6 by 5 cm. The capsule was thick and densely adherent, except at points where abscesses reached the surface. The cortex and medulla were still distinguishable in

spite of the fact that the kidney was so riddled with abscesses as to scarcely hold together. The left kidney measured 8 by 3 by 1 cm. The lower pole was perforated by the drainage tract. The capsule was thick and very adherent, and throughout the parenchyma were many abscesses. The pelvis was large and baggy, the wall thickened, and the mucosa discolored by petechial hemorrhages. The ureters were tortuous and dilated until they entered the pelvic mass, which definitely constricted them.

The uterus measured 8 cm. in length and 4.5 cm. across the fundus. The myometrium averaged 2 cm. in thickness. The cervix was small and symmetrical. In the right side of the vesicovaginal septum were two purple elevations 1 to 1.5 cm. in length. On section, these were filled with a dark brown fluid. The mass constricting the ureters was composed of interlacing fibers, among which were small brown masses and minute open spaces. The portion of the mass encroaching upon the rectum was gray and dense.



Fig. 2.—Glands surrounded by stroma present in pelvic mass.

Microscopic Examination.—The glomeruli of the right kidney varied greatly in size, but were the least involved of the renal structures. The epithelium of the tubules was flattened and the lumina were distended with white blood cells. The connective tissue was increased. The organ was massively infiltrated with polymorphonuclear leucocytes. The increase of connective tissue in the left kidney was greater than in the right. The cellular infiltration was dominantly lymphocytic. The tubules, lined by a low, much vacuolated epithelium, were dilated, and for the most part empty.

Each ureter, with the mass surrounding it, was sectioned in one piece. The muscular coats of both ureters were hypertrophied. Sections of the ureters taken above the pelvic mass showed an intense infiltration of the submucosa, and to a lesser degree of the muscular layers, with lymphocytes and plasma cells. The lumen of the left ureter, where it passed through the pelvic mass, was almost obliterated, and was devoid of epithelium.

Sections taken through the indurated mass, which practically obliterated the culdesac and girdled and constricted the ureters, showed smooth muscle and con-

nective tissue traversed by small capillaries. Scattered throughout the muscular and connective tissue structures were irregularly dilated glands lined by low columnar cells, whose large, dark oval nuclei almost filled the cytoplasm. No mitosis was observed. (Fig. 2.) The basement membrane was intact. In certain of the glandular cavities irregular granular particles of brown pigment and shadows of red blood cells were seen. Free and phagocytized pigment was also found in the stroma. In some sections the glandular structures lay free in a bed of dense fibrous tissue; in others, they were surrounded by a varying quantity of loose stroma, the cells of which contained oval nuclei, with regularly distributed chromatin. (Fig. 3.) The loose stroma definitely resembled that of the uterine mucosa. A few disintegrating columnar epithelial cells were found in the clot attached to the broad ligament.

Sections through the uterus showed the endometrium and myometrium clearly demarcated. The glands of the former were small and characteristic of the resting stage. The myometrium showed the usual tortuous pattern of smooth muscle and a slightly increased quantity of connective tissue. The cyst found in the vault of the vagina was lined by cuboidal epithelium, which at certain places was three

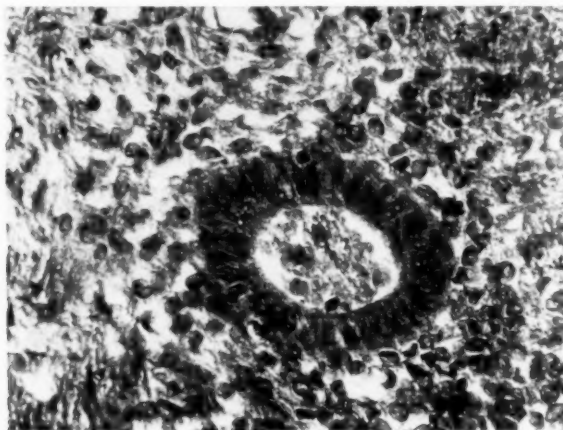


Fig. 3.—High power microphotograph of gland and stroma present in pelvic mass.

to four cells deep. The cervical epithelium was hyperplastic and in the wall of the cervix were two small cysts lined by flattened epithelium. One of these cysts contained old blood.

Sections of the ovaries showed a corpus hemorrhagicum and several corpora albicantia. No endometrial tissue could be demonstrated. Sections of the tubes showed nothing worthy of note.

Anatomic Diagnosis.—Pelvic endometrioma involving the parametrial tissues and constricting the ureters; chronic cystitis; ureteritis, pyelonephritis, bilateral, recent operation (pyelotomy, left); metastatic abscesses of lung and spleen; emaciation.

SUMMARY

The clinical history and the postmortem findings are given in the case of a patient who was under observation over a period of five years for a diffuse pelvic lesion. This was complicated later by a bilateral renal involvement which led to death. There were no changes within the uterus itself. It was distorted by the mass of dense tissue which

fixed all the pelvic structures and encroached upon and constricted the lumina of the rectum and ureters. A histologic study of this indurated mass showed it to be made up for the most part of connective tissue, throughout which were scattered irregularly dilated glands lined by low columnar epithelium. Some of these glandular structures lay free in a bed of fibrous tissue, while others were surrounded by a varying quantity of loose stroma. In some of the gland lumina irregular granular particles of brown pigment and shadows of red blood cells were seen.

From the histologic study of the specimens, we believe that we are dealing with an unusually diffuse type of endometrioma. The structure of the glands is quite like that found in the uterus, while the epithelium lining the glands and the stroma surrounding them is similar to that found in the endometrium. Moreover, the presence of pigment and of shadows of red blood cells in the gland cavities indicates that these ectopic structures underwent the physiologic changes which characterize the menstrual cycle. Further evidence that this activity took place is found in the fact that the acute attacks of pain were associated with the onset of the menstrual period. Similarly, the recurring pain in the legs doubtless resulted from pressure by the swollen tissues upon the pelvic nerve trunks. That the cells were deposited from a secondary endometrial cyst of the ovaries is ruled out by the relatively normal structure of these organs. It seems, therefore, that the original epithelial structures may have come, as Sampson has suggested, either from the mucosa of the tubes or by transportation from the cavity of the uterus. Finally, it is clear that the bilateral renal lesions depended primarily upon the presence of the pelvic endometrioma, which had gradually encroached upon and constricted both ureters.

THE ANATOMY, GENESIS, AND CLINICAL CONSIDERATIONS OF PLACENTA ACCRETA*

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AN ORGAN whose structure is so complex, and which is so highly endowed with many varied and important functions as is the placenta, would appear to be subject to the frequent occurrence of pathologic variations. This in turn seems to be favored by the remarkable rapidity of its growth to maturity, and in fact senility, in such a short time as ten lunar months.

This communication deals with that rare placental anomaly designated as placenta accreta and the extremely disastrous results which may accrue from failure to recognize the lesion, and the consequent institution of incorrect measures to counteract the complication. There are also many clinical and anatomic considerations connected with placenta accreta, some of which are still mooted, so that a discussion of these in the light of recent studies together with those involved in the case to be presented, should, it is hoped, prove of some interest.

I desire to preface the case report by expressing my gratitude to Dr. Nathan Ratnoff, for the rare privilege of allowing me to study this case which occurred on his service.

CASE REPORT

Mrs. L. F., Hebrew, para ii, aged thirty-seven, admitted to the Jewish Maternity Hospital, June 7, 1925, in active labor. Her previous medical and surgical histories were essentially negative. Her first pregnancy terminated in a stillbirth at term in July, 1924, of undetermined cause. No difficulty was encountered in the delivery of the placenta, and no complications occurred in the puerperium. The patient was a short, rather stout woman at term, whose general condition was excellent. Pelvic measurements were ample. The head was engaged in the L. O. A. position, but the fetal heart was not heard at the time of the patient's admission to the hospital, nor at any time throughout her labor. She was delivered of a still-born female child five hours after admission. Following the delivery of the child, the placenta did not come away. It is important to note that no bleeding was present at this time. In view of the fact that at the end of three hours, the placenta was still within the uterine cavity, and no bleeding had occurred, the possibility of an adherent placenta was suspected. Four hours after the birth of the child, the uterine cavity was explored under anesthesia, under the strictest aseptic precautions, and while small parts of the placenta came away on the examining hand, no line of cleavage could be detected. No further intrauterine manipulations were attempted, and a diagnosis of placenta accreta was made. The uterine cavity was tightly packed with iodoform gauze. Hysterectomy, which was advised, was agreed to by the patient, and the operation was performed eight hours after the delivery of the child. The operation was easily carried out, only the uterus being removed. The patient reacted in a satisfactory manner, and after an uneventful convalescence, was discharged in excellent condition, fifteen days postpartum.

*Read, by invitation, before the Section on Obstetrics and Gynecology, New York Academy of Medicine, April 26, 1927.

Pathologic report by Dr. Alfred Plaut, Pathologist of the Woman's Hospital, New York City.

Gross.—The specimen which had been in some fixing fluid for about two years has the following gross aspects. Open uterus with a large mass of placental tissue protruding from the opening. The longest diameter of the specimen is 17 cm., the two others are 12 cm. and approximately 7 cm. The specimen is quite distorted and does not show the landmarks for easily establishing the site of the fundus and cervix. Probably the shorter diameter corresponds to the axis of the body of the uterus. The placenta is chiefly attached to the upper part of the corpus. The average thickness of the uterine wall is 5 cm. Spongy placental tissue and firm myometrium can be seen on the cut surface in direct continuity with each other and without any demarcation line between them. Additional cut surfaces



Fig. 1.—Section from a case of placenta accreta, showing the attachment of the placenta in direct continuity with the myometrium, *without* the interposition of a spongy layer of the decidua basalis, and the invasion of the myometrium by the chorionic villi.

give essentially the same picture. At other points, however, the fixed tissue when it is bent breaks at the junction of the placenta and myometrium. The cut surfaces of the placental tissue itself show nothing particular, neither do the cut surfaces of the myometrium. *At the attachment of the placenta, the average thickness of the myometrium is only about 2 cm.*

Microscopic.—In several sections, the chorionic villi and the masses of the trophoblast are seen to be directly situated upon the myometrium, *without* a spongy layer intervening. The invasion of the chorionic elements does not go deeper into the muscle than it frequently does even in normal placentation. At several points necrosis and hyalinization of placental tissue are seen. There are also small areas of calcification. Sections far away from the placental site show the usual wide Opitz glands and partly edematous decidua between them.

Diagnosis.—Placenta accreta.

Incidence.—From a study of the literature, the frequency of placenta accereta can be said to be controversial. Statistics vary from one in six thousand cases as reported by Polak, to one in forty thousand cases, as stated by B. C. Hirst. In a personal communication, Dr. Harold Bailey informed me that in over twenty years' experience on two active teaching services, he has seen three cases of placenta accereta. While no doubt many obstetricians may lay claim to having seen cases of placenta accereta, they fail to give the essential details of the gross, and particularly the minute, anatomy by which alone the diagnosis can be determined, and the claim to placenta accereta be substantiated. Such frankly missed or unconfirmed examples may well amount to a considerable number of cases, while the true nature may be suspected, but they are not sufficiently definite to warrant publication.

The failure of practitioners to report cases, and the variations in their correct interpretation of the condition seemed to warrant an attempt to determine if possible, the approximately correct incidence of the lesion. To that end, therefore, a study was made of its occurrence in the obstetric services of the Jewish Maternity Hospital, the Woman's Hospital, and the Berwind Maternity Clinic, all of New York City. In a collective series of about seventy-five thousand consecutive cases, four cases of true placenta accereta have been encountered. Thus it would seem that a fairly correct estimation of the incidence of the condition would place it at about one in twenty thousand cases. A study of the literature by the writer has shown nine authentic cases to have occurred since 1924, giving a total of thirty-six cases reported to date.

ANATOMY

Placenta accereta is represented by a definite anatomic-histologic picture. Macroscopically, the placental base is thinned out in practically its entire course. Hence the predisposition to rupture of the uterus even on the slightest manipulation is readily explained on this anatomic defect. While in Dietrich's case the uterine wall is nearly completely absent, such is not the finding in our specimen and in the majority of cases reported to date.

Microscopically, the factor which is essential in order to designate the lesion as a placenta accereta, is the insufficient development or entire absence of the decidua basalis, which defect must be demonstrable beyond a doubt, so that the placenta is found to be inserted directly on the muscularis, *without* the interposition of a mucous membrane, with or without a direct invasion of the myometrium by the chorionic villi. Hence, on etymologic grounds, I would suggest that the term *accreta* be applied to the lesion when the former condition is present, and *increta*, when in addition to the defective or absent basalis, the villi are found to invade the muscularis of the uterus. It will thus be seen that the anatomic aspects of the problem explain very adequately that the diffi-

culty in the separation of the placenta is due to a faulty fragility of the placental base, in turn due to the penetrative attachment of the organ.

GENESIS

In order to appreciate the processes which are operative in placenta accreta, it would perhaps be in order to briefly recall the mechanism of the normal separation of the placenta. In 1875, Langhans demonstrated that the placenta does not loosen in the compact layer, but at the junction of the compacta and spongiosa. Hence, it follows that any alterations from the normal in the embedding of the placenta will be productive of difficulty in its separation.

Since it is recognized that the change in the structure of the decidua basalis or the lack of the mucosa of the basalis is the reason for the difficult separation, it is necessary to understand why the placental site shows these changes. Hinselmann, who has made an exhaustive study of the subject under discussion, feels that the first step in this direction is the examination of the decidua vera. But unfortunately, as he points out, the decidua vera is only rarely examined. In the case reported by Dietrich in 1922, it was found to be completely lacking. It is also pointed out that Robert Meyer emphatically does not speak of a parietalis (decidua vera). Similarly, Newmann has examined a deep-seated placenta and is not very certain that he had examined portions outside of the placental base. While in our case, sections far away from the placental site showed partly edematous decidua, we are not inclined to draw any conclusions on the basis of one case.

Hinselmann, however, offers the following statement. In the cases of a normally situated placenta accreta in which the parietalis is examined, it is either not demonstrable or it is extremely rudimentary. In the cases of deeply situated placenta accreta the parietalis of the higher sections of the uterus has been found to be normal in several cases. He is, therefore, led to distinguish the following two categories:

1. The normally situated placenta accreta. In this connection he raises the question that after the absence of a basalis has found its analogue in a lack of or excessive reduction in the parietalis, did this reduction of the parietalis exist at the beginning of pregnancy or did it occur in its course? A logical answer to this can only be derived from clinical observations. The fact that many of the women have a history of repeated manual separation would make it appear that there must be some persistent underlying cause. He, therefore, feels that a mucosal change was already present prior to the onset of pregnancy. On the other hand, the condition of the mucosa in the interval of pregnancy cannot be satisfactorily answered by clinical experience, since other factors, especially ovular ones play a rôle. The question as to whether it is not a congenitally unsuitable mucosa cannot as yet be answered, but from the information at hand it seems unlikely.

The majority of writers feel that while the first manual separation was performed for other reasons than placenta accreta, nevertheless the manual separation so reduced the uterine mucosa, that it did not regenerate to its normal thickness.

Similarly, frequently repeated curettages, deep-seated infectious processes which follow manual separation, as well as instrumental curettage of the uterine cavity in the gravid state, and particularly in early puerperal cases are especially to be feared. Hence, it is fair to state that all of these causes unite themselves to produce deleterious results as manifested by an unfit placental base with the consequent penetrative attachment of the placenta.

2. In reference to the deeply situated placenta accreta, the principles just described hold true, since here also the mucosa is found to be thin, thus predisposing to the development of placenta accreta.

It is also claimed by some writers that the tubal angles and the lower uterine segment show a predisposition to placenta accreta on account of the thinness of the mucosa in these regions. In like manner, submucous myomas are referred to as favoring the development of placenta accreta. In this connection, Hinselmann quotes Frankl's investigations on the reaction of the mucosa in centripetally growing interstitial and submucous myomas, which lead to a reduction of the mucosa, and as pointed out by these writers, in the cases of the submucous type of growth, one can speak at times only of a covering epithelium. Hence, there also exist in the lesions just mentioned, conditions suitable for the formation of placenta accreta. Similarly, it is claimed that the septum of a uterus bicornis unicollis and the rudimentary accessory horns of the uterus possess the adaptability to the development of accreta.

Before leaving this part of the subject, one must call attention to the fact that a study of the literature shows that theoretically, at least, placenta accreta is possible at any period of gestation after the third month, since Tennant's case occurred in the fifth month of pregnancy. In the case reported by this writer and his collaborators, it was demonstrated that the placental attachment may not alone invade the peritoneal coat of the uterus, but actually invades the visceral cavity. In this case, from the appearance of the crater where the placenta extruded through the uterine wall, one can readily see the possibility of the growth extending over and into the bladder, bowel, and mesentery.

Tennant's case concerned a para v, with a history of four previous manual separations of the placenta. In her fifth pregnancy she was treated for a threatened miscarriage in the fourth month, and one month later miscarried. As the placenta would not come away spontaneously, manual removal was attempted but without success. There was no bleeding for thirty-six hours, at the end of which time exploration of the uterine cavity showed that no line of cleavage could be found. Hysterectomy was advised but was refused by the patient, and she died of acute sepsis at the end of eight days. At autopsy, the placenta was found adherent to the vault of the uterus, and had grown through its wall which was found to be exceedingly thinned out at the point of attachment of the placenta, only the peritoneal coat being left.

CLINICAL CONSIDERATIONS

Polak has pointed out the characteristic clinical findings in placenta accreta. Separation of the normal placenta does not occur without bleeding. He, therefore, emphasizes this in giving the differential diagnosis between the simple retention of a separated placenta and placenta accreta. In the former, three clinical signs are always evident: (1) uterine bleeding, (2) descent of the umbilical cord, (3) the characteristic ball-like condition of the fundus. Conversely, provided there has been no manipulation to cause partial detachment of a placenta accreta, there is neither hemorrhage, descent of the umbilical cord, nor changes in the position of the fundus, the latter assuming a characteristic shape, which as pointed out by Polak causes it to be broader from side to side, intermittently relaxed, and *not* assuming the ball-like shape characteristic of the normal placenta which has separated.

In this connection one would call attention to the differentiation of accreta from the so-called adherent placenta, which is due to a disturbance in the mechanism of separation, and not to an anatomic defect. Here the line of cleavage is always found, and manual removal is not usually attended with great difficulty.

Hence, in the presence of a delayed delivery of the placenta, particularly in the absence of hemorrhage, the attending obstetrician should be on the *qui vive* for the possible existence of placenta accreta. If after a reasonable length of time the clinical signs of separation enumerated above are not present, no attempt at Credé delivery should be made. Immediate steps should be taken to explore the uterine cavity under the strictest aseptic precautions under anesthesia, to determine what subsequent measures should be instituted. If upon entering the uterine cavity no line of cleavage is found to exist between the placenta and the uterus, hysterectomy is the only rational procedure, for by this alone can rupture of the uterus be avoided and the patient saved from death which usually follows this catastrophe, as a result of hemorrhage or sepsis.

To substantiate this assertion, one need only assemble the cases reported within the past few years. In practically every one in which attempts to separate the placenta in the presence of an accreta were made, the patient succumbed either to hemorrhage, shock, or sepsis. Of the three cases seen by Polak the only recovery occurred when supravaginal hysterectomy was performed. We attribute the satisfactory outcome in the case here reported to the prompt recognition of the accreta, and the performance of hysterectomy without the previous institution of meddlesome maneuvers.

In the discussion of Polak's paper, Frankl unqualifiedly subscribed to the tenet that in a case of anatomic placenta accreta, the indication is definite for extirpation of the uterus. As a proof against the futility of attempting to separate the placenta, and resorting to less radical

treatment than hysterectomy, as advocated by B. C. Hirst and others, Frankl cites two cases in which he had performed postmortem examinations. It was found absolutely impossible to separate the placenta from the uterine wall. It is, therefore, justifiable to assume that the high mortality hitherto reported has been due, it would seem, to the expectant or supportive treatment, since twenty-four of the twenty-six cases reported up to 1924, resulted in the death of the patient.

SUMMARY AND CONCLUSIONS

As a result of this study, the opinion may be confirmed that although placenta accreta is a rare obstetric anomaly, it possesses definite anatomic-histologic properties as reflected by a defective or absent spongy layer of the decidua basalis. The incidence of the lesion is about one in twenty thousand cases. The frequency in the history of abnormal detachment of the placenta would suggest that any condition which leads to an atrophy of the endometrium is a predisposing factor to the development of placenta accreta. At the same time, the possibility must be entertained that the fault may lie in an improper development of the corpus luteum, since it is known that this is the factor which controls the normal development of the decidua.

Unless previous manipulations have been made to cause partial detachment of the placenta, the condition is recognized by a failure at separation of the placenta, and by an absence of bleeding. This is corroborated on exploration of the uterine cavity by a failure to find a line of cleavage between the placenta and the uterus whenever placenta accreta is present. As soon as the diagnosis has been made, hysterectomy is the only rational procedure, for this offers the best hopes for the patient's life, and is the most favorable in reducing the mortality of this very serious obstetric complication.

I desire to express my sincere appreciation to Dr. Alfred Plaut and Dr. Morris Dreyfuss of the pathologic department of the Womans Hospital, New York City, for their kindness in examining the microscopic sections, and for much valuable aid in this study.

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A REVIEW OF ONE THOUSAND AND ONE OBSTETRIC CASES*

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FROM October 1, 1925, to December 31, 1926, there were admitted to the Jewish Maternity Hospital 1001 pregnant women who were delivered of 1014 infants. Of these patients 460 were private cases and 541 were ward cases.

The private cases were attended by the members of the staff and by other physicians to whom the courtesy of the hospital had been granted.

The work in the wards, with the exception of the complicated cases, was conducted by the chief resident physician, and the interns under his supervision.

The ward patients, with the exception of an occasional emergency case, registered previous to their admission to the hospital and received careful prenatal care.

Of these patients who attended regularly the prenatal clinic, none developed eclampsia. There were, however, 18 patients admitted with preeclamptic symptoms, such as a rising blood pressure, albumin and casts in the urine, headache, dimness of vision and edema. Of these patients 12 were ward and 6 were private. Of these 18 patients, 5 were delivered of twins.

A list of presentations and positions are shown in Table I.

TABLE I. PRESENTATIONS

Vertex	974	
Anterior position	812 or 80 %	
Posterior position	156 or 15.4%	
Face	6 or 0.6%	
Breech	31 or 3.1%	
Transverse	4 or 0.4%	
Unrecorded	5 or 0.5%	

Of the 1001 patients 738, or 73.8 per cent, had normal deliveries. The number of patients delivered with forceps was 234, or 23.4 per cent.

TABLE II. METHOD OF DELIVERY

Normal delivery	738 cases
Cesarean section	5
Version	24
Forceps	234
Total	1001

*Read at a meeting of the Obstetrical Society of Philadelphia, October 6, 1927

TABLE III. FORCEPS DELIVERIES

Private patients	460	Ward patients	541
High forceps	4	1	
Mid forceps	53	30	
Low forceps	77	59	
After-coming head	10	0	
	144, or 31%	90, or 16%	

Forceps.—From Table III it is evident that the total percentage of forceps deliveries is rather high. However, the 16 per cent of forceps deliveries in the ward patients contrasted with 31 per cent in private patients demonstrates emphatically what may be accomplished by watchful waiting and allowing nature its full opportunity.

Watchful expectancy, however, must be tempered with good judgment and in the presence of distinct indications, nature should be assisted promptly.

The indications for the so-called prophylactic forceps seem to be more numerous and more urgent in private patients.

Version.—Twenty-four patients, or 2.4 per cent, were delivered by podalic version, as shown in Table IV.

TABLE IV. VERSION—INDICATIONS

Premature separation of placenta	1
Occiput posterior	5
Prolapsed cord	5
Placenta previa	5
Twins	4
Heart disease	1
Time	3
	24

Infant mortality 5, or 20.8 per cent. In these cases of version there were 5 infant deaths, a mortality of 20.8 per cent. One infant death occurred five days after delivery in a seven and a half months' gestation in a mother who had a mitral stenosis and a lobar pneumonia. The second death was in a case of central placenta previa and the third in a case of marginal placenta previa. The fourth fatality was in a case of prolapsed cord. The fifth death was in a case of premature separation of the placenta. The mother was moribund when admitted and a version was done with the remote possibility that the child might be saved.

Cesarean Section was performed on only five patients, or one in 200 cases, without a maternal or fetal death. The indication in all cases was a contracted pelvis and the classical operation was performed.

The complications encountered in these 1001 cases were as follows:

TABLE V. COMPLICATIONS

	NO. CASES	STILLBORN	INFANT DEATH
Placenta previa	8	2	0
Premature separation of placenta	6	2	1
Prolapsed cord	10	2	1
Contracted pelvis marked	10	1	0
Preeclampsia	18	8	0
Cardiac disease of mother	47	0	1
	99	15	3

In these 99 complicated cases there were 18 infant deaths, a mortality of 18 per cent.

Placenta Previa.—The 8 cases of placenta previa consisted of 1 central and 7 marginal previas. All occurred in multipara. Of these, 5 were delivered by podalic version with 2 fetal deaths, and three were delivered with forceps. The case of placenta previa centralis had been packed and the fetus was dead when the patient was admitted. Of the 7 cases of previa marginalis, 2 were treated by Voorhees bags and forceps; 4 had vaginal packing and version with one infant fatality; one had vaginal packing and forceps.

Premature Separation of Placenta.—There were 6 cases of premature separation of the placenta. Of these cases, 4 were delivered with forceps; one by podalic version and one with a breech presentation had a spontaneous delivery.

In these cases there were 3 fetal deaths; two were in cases delivered by forceps and the third fatality was in the version delivery; the mother being moribund when admitted.

Prolapsed Cord.—There were 10 cases of prolapsed cord. Of these, 2 were forelying cords, palpable through the os, but in the intact bag of waters. In the other 8, the cord was prolapsed into the vagina. Of these 10 cases, 5 were delivered by version, with one fetal death; 2 were delivered with forceps, with 2 deaths. In the remaining 3 cases the cord was replaced and the delivery was spontaneous.

Contracted pelvis (marked).—There were 10 cases of marked contraction of the pelvis. Nine of these patients were given a test of labor. The tenth patient had an elective cesarean section. Of these 10 cases 5 were delivered by cesarean section, the other 5 were delivered with forceps, with one fetal death.

Among these 1001 cases there were 10 patients who had had cesarean sections in other institutions for pelvic contraction. They were advised to go into labor and all were successfully delivered by forceps of normal babies.

Preeclampsia.—There were 18 patients admitted with preeclamptic symptoms. The treatment consisted of rest in bed, strict diet, free purgation, 20 c.c. of a 10 per cent solution of magnesium sulphate intravenously repeated as often as was necessary. Patients with a blood pressure of 200 or above, had a venesection.

The patients in whom the toxemia was progressive had labor induced by the Voorhees bags. The remaining 16 patients had a spontaneous labor. In these preeclamptic patients there were 8 infant deaths which were classified as follows:

Premature spontaneous	2
Macerated spontaneous	3
Full-term spontaneous	1
Induction—Voorhees bags	2
	<hr/> 8

Cardiac Disease in Mother.—In these 1001 mothers there were 47 who had pronounced cardiac lesions. The treatment consisted of absolute rest in bed for several weeks before the delivery and such medication as was necessary; each case being individualized. These patients were allowed to go into natural labor. Morphine and scopolamine or morphine and magnesium sulphate were given during the period of dilatation. At the end of the first stage of labor under light anesthesia the deliveries wherever possible were completed. The methods were as follows:

Normal	12
Forceps	34
Version	1
	<hr/> 47

After delivery these patients were kept in bed for at least four weeks or longer if necessary.

In these 47 cases there was one fetal death in a patient who had pneumonia and a mitral stenosis. The baby lived five days.

Morbidity.—In computing the morbidity we have considered that every patient who had a temperature of 100.4° F., twice in one day excluding the first twenty-four hours, to be morbid. Among the 1001 patients there were 40, or 4 per cent who had abnormal temperatures. In this connection it is interesting to note that the morbidity in the private patients was 5 per cent while in the ward patients it was only 2.9 per cent.

The higher morbidity among the private patients may be explained by three factors. First, the private patients were usually examined more frequently *per vaginam*. A ward patient seldom had a vaginal examination, the progress of labor being followed by rectal examinations. Second, the private patients were not only delivered by members of the staff, but by many nonstaff doctors to whom the courtesy of the hospital had been granted and whose technic was varied. The ward patients were delivered by members of the staff only and the technic was uniform. Third, there was decidedly more interference with labor among the private cases than among the ward cases. This traumatism from interference was probably the largest factor in the higher morbidity among the private patients.

Infant Mortality.—The infant mortality has been classified as follows:

	STILLBORN	INFANT DEATHS
Macerated	16	0
Premature operative	0	1
Premature spontaneous	4	5
Full-term operative	9	7
Full-term spontaneous	3	4
	<hr/> 32	<hr/> 17

Of the 1014 infants delivered there were 49 deaths, a mortality of 4.8 per cent. The fetal mortality would be reduced to 3.2 per cent if the 16 macerated infants were eliminated.

Maternal Mortality.—The maternal mortality in these 1001 cases was 2, or 0.2 per cent. The first fatality was in an elderly multipara who was told at another hospital that she had a premature separation of the placenta and should have a cesarean section. She left the hospital against advice. She continued to bleed for forty-eight hours more and was then rushed to the hospital, was moribund when admitted and died twenty minutes later.

The second was in a multipara, with advanced mitral stenosis and decompensation. She had disregarded the prenatal advice of her physician and he refused to continue with the case. When admitted she had a right lobar pneumonia. She was delivered by podalic version and died forty hours later of cardiac failure. The baby lived five days.

The first fatality should be excluded as the patient was moribund when admitted. With this patient eliminated the actual mortality was 0.1 per cent.

It might be interesting to note that during the time these 1001 patients were being treated there occurred at one time in the nursery many cases of what appeared to be clinically an abortive form of simple impetigo (pemphigus neonatorum). Cultures of these cases were either sterile or showed a staphylococcus of low virulency. The first few cases were mild in character, but later cases seemed to be more virulent and less amenable to treatment. The attending dermatologist, Doctor S. Greenbaum, who investigated the condition suggested that liquor cresolis comp., which was being used freely around the hospital might be the cause of the irritation. Following his recommendations, the use of that antiseptic was discontinued and the cases gradually disappeared. From then on there has been no recurrence of this condition.

Postpuerperal.—The patients before being discharged were invited to return to the postpuerperal clinic in from four to six weeks for examination and any necessary treatment. Many of the patients returned voluntarily and others were sent in by the Social Service Department. By these means it has been possible to keep a follow-up on 80 per cent of the clinical cases. Of the 432 patients who returned to the post-

puerperal clinic, lacerations of the perineum were found in 272, or 63 per cent. Lacerations of the cervix were found in 391, or 90 per cent.

In the first 100 patients who returned to the postpuerperal clinic, 39, or 39 per cent, had retrodisplacements of the uterus. It was then decided to eliminate the abdominal binder at the end of twelve hours and to have the patient lie on the abdomen a considerable time each day. After the tenth day the patients, with empty bladders, were placed in the genupectoral position for ten minutes morning and night and were instructed to continue with the treatments until they returned to the clinic.

After these changes had been made, retrodisplacements were found in 73 of 332 patients, or 22 per cent, a reduction of 44 per cent. Of the 112 cases of retrodisplacements, 65 were cured by restoring the organ to its normal position and by the continuation of the genupectoral position morning and night. The remaining 47 patients had pessaries inserted, 9 of these under gas anesthesia. Of the 47 pessary cases 21, or 45 per cent, were cured. In the remaining 26 cases when the pessaries were removed several months later, the uterus returned to the posterior position. Of this group in 12 cases the displacements caused no symptoms, while 14 had well marked symptoms.

Of the 112 cases of retrodisplacements of the uterus, 86, or 77 per cent, were cured.

CONCLUSIONS

Careful prenatal care as carried out in all well-regulated clinics, saves many patients later complications and reduces maternal and fetal mortality.

Watchful waiting and allowing nature its full opportunity will diminish the incidence of forceps deliveries and extensive lacerations.

The majority of cases of placenta previa can be successfully treated conservatively. Only a very small percentage of cases require cesarean sections.

Contracted pelvis are only relative and much depends on the size and position of the child. Unless there is a decided disproportion, the patient should be given a real test of labor before a cesarean section is elected.

Pregnant women with cardiac diseases should be treated by prolonged rest in bed, proper medication and analgesic remedies during the first stage of labor and then delivered with forceps under light anesthesia.

Elimination of the abdominal binder after twelve hours, position and exercises will materially reduce the number of retrodisplacements of the uterus.

The postpuerperal supervision and care of the patient is most beneficial and should receive more earnest and efficient attention.

TEN YEARS' EXPERIENCE WITH GYNOPLASTIC REPAIRS OF OLD LACERATIONS FOLLOWING CHILDBIRTH, WITH REPORT OF 1019 CASES*

BY J. L. BUBIS, M.D., F.A.C.S., CLEVELAND, OHIO

ANY new or radical procedure from the orthodox methods is always viewed with scepticism and distrust. It takes time, experience, and the evidence of final results to prove whether the change advised is safe and justifiable. What was radical and dangerous a generation ago, can now be done in safety and with satisfactory end-results, due to the remarkable progress that medicine has made since the discovery of asepsis, antisepsis, and anesthetics.

Has obstetrics kept pace with and made use of this progress and advancement? The laity, general practitioners, and even many obstetricians do not realize that childbirth should be given the same consideration as major surgery and that the obstetric case is entitled to and should demand the benefits resulting from surgical progress. We hope that the day will come when every woman can be delivered under anesthesia in a well-regulated hospital, so that the results that we have obtained can become universal.

It has been our routine for many years to examine the cervix, vaginal walls and perineum after the expulsion of the placenta for old as well as new lacerations and to repair them as soon as possible. The present review deals with a report of 1019 cases which were operated during the past ten years by the obstetric staff at Mount Sinai Hospital of Cleveland. Our observations have proved that about 50 per cent of the multiparas delivered were in need of gynoplastic repair for old lacerations. (Table I.) During the last five years, the ages of patients operated varied from 18 to 47 years (Table II), and the parity varied from ii to xiv (Table III).

TABLE I. OBSTETRIC ACTIVITY AT MOUNT SINAI HOSPITAL IN 1926

Total admissions		886
Primiparas	373	
Cesarean sections; obstetric complications, as eclampsia, heart or kidney disease; multiparas that did not need repairs or refused to have them done, etc.	340	
Total	713	713
Multiparas repaired		173
i.e. 19.5% of total admissions in 1926 were repaired, or 33.% exclusive of the primiparas		

*Read before the Chicago Gynecological Society, Meeting of November 18, 1927.

TABLE II. AGE

Para ii

	18	19 to 24	25 to 28	29 to 32	33 to 37	38 to 47
1922		19	35	51	49	16
1923		14	36	63	28	20
1924	1	22	45	59	60	20
1925		23	36	46	39	18
1926		18	46	51	42	16

TABLE III. PARITY

YEAR	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIV
1922	68	51	22	16	4	4	2	1	1			
1923	60	50	23	9	11	4	3					
1924	82	51	28	16	15	3	4	4	2	1		1
1925	61	35	28	13	8	4	4	5	1	1	2	
1926	52	51	30	16	14	5	1	2	2			
Total	323	238	131	70	52	20	14	12	6	2	2	1

TABLE V. TYPES OF DELIVERIES FOLLOWED BY GYNOPLASTIC REPAIRS FOR OLD LACERATIONS

	PR.	SP.	L. F.	M. F.	V. E.	BR.	DIL. C. L. F.	MAC. F. L. F.	SC. M. F.	DIL. C. M. F.	BAG BR.	DIL. C. V. E.
1922		99	54	5	8	3						
1923		100	34	2	11	3	2	1	4		1	1
1924		106	48	10	14	3			4	3		3
1925	5	88	42	9	12	2			2	1		1
1926	1	108	32	7	12	4			5	1		3

Pr., Precipitate. Sp., Spontaneous. L. F., Low forceps. M. F., Mid forceps. V. E., Version and Extraction. Br., Breech. Dil. C., Manual dilatation of cervix. Mac. F., Macerate fetus (afebrile). Sc., Scanzonian maneuver.

TABLE VI. DAYS IN HOSPITAL FOR DELIVERY AND REPAIR

	4 TO 10 DAYS	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25 TO 43 DAYS
1922					32	39	36	18	27	9		4	2	2		
1923	5	6	11	14	20	31	26	14	7	6	7	5	3		1	2
1924		2	1	11	25	33	49	31	20	8	6	3	3	2		6
1925	3	6	3	10	38	11	22	25	14	7	5	2	6	2	1	
1926	7		8	11	24	30	28	24	12	8	5	5	2	3	2	1

Both new and old lacerations have been repaired immediately or within a few days with little additional danger to the mother (Table IV). Contrary to general belief the tissues can be easily recognized, and lochia, edema and operative deliveries do not seem to interfere with the results of the repair (Table V). In our experience subsequent deliveries are not complicated by previous repairs. If new lacerations occur they are treated like primary lacerations. The patient's stay in the hospital is not greatly prolonged (Table VI). The technic indications and contraindications have been fully described in my previous articles.¹ The types of operations performed are shown in Table VII. Table VIII shows the temperature of cases operated during 1926. Complications that occurred in the same year are shown in Table IX.

TABLE IV. TIME OF REPAIR OF OLD LACERATIONS AFTER DELIVERIES

YEAR	IMMEDIATELY	NEXT DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY	9TH DAY	10TH DAY	11TH DAY	12TH DAY	13TH DAY	14TH DAY	TOTAL CASES
1922	156	1	1	4	2	4	1								169
1923	119	2	11	5	15	3	2	3			1				161
1924	167	2	8	13	13	1	1				1			1	207
1925	129	5	3	10	3		7	4			1				162
1926	152		4	4	5	2	4		1	1					173
Total	723	10	27	36	38	10	15	7	1	1	3			1	872

TABLE VII. TYPES OF OPERATIONS

YEAR	C	T	P	H	TP	TC	TCP	TPH	TPU	TCH	TCPH	CPH	CP	ACP	ACPH	AC	PH	AMP C P
1922		29	43	3	71	1	7	4				1	10					
1923	1	25	47	2	53	1	11	1	1	1	6	3	4	3	2		1	
1924	1	26	43	8	79	2	20	9		3	5	4	1	2	1	1	2	
1925		20	58	7	45	1	10	9			1		8				3	
1926	4	16	63	9	47		7	3			5	1	8	1			8	1

C., Cystocele. T., Trachelorrhaphy. P., Perineorrhaphy. H., H. morrhoidectomy. AC., Partial amputation of cervix. U., Umbilical hernia.
AMP. C., Total amputation of cervix.

TABLE VIII. TEMPERATURE CHART FOR 1926
127 OR 71.6% OF THE 173 CASES RAN AN AFEBRILE COURSE, I.E., BELOW 100° F.

100° or over No. of days	No. of cases
1	11
2	6
3	2
4	2
5	2
6	1
7	5
9	4
10	11
13	1
43*	1

*Died.

TABLE IX. COMPLICATIONS IN 1926

	NO. OF CASES
Shock	3
*Severe bleeding	3
Bronchopneumonia	1
Aspiration during anesthesia	1
Bronchitis	1
Cystitis	3
Cystopyelitis	8
Parametritis	2
Edema of vulva	1
Slough of perineum	2
Retained blood clot	2
†Septicemia	1

*One patient had a partial placenta previa and was transfused the next day.

†Died.

In the series of 1019 cases there were two deaths one of which was reported in my last paper.² The history of the second case is as follows:

Mrs. K. W., aged forty-two years, para vi, was admitted to the obstetric service on April 16, 1926. Examination on admission showed the fetus in a transverse position, the membranes ruptured and the cervix two fingerbreadths dilated. April 17 at 2 A.M., the head was still unengaged. Version and extraction were done and an eleven-pound child was delivered after forty hours of labor. Three days later, the patient was taken to the operation room and a badly lacerated cervix, a marked cystocele and rectocele were repaired. Considerable hemorrhage took place, necessitating much suturing and prolonged anesthesia. April 22 to 24, the patient complained of weakness, headache and chills. She had a septic temperature ranging from 100° to 104° F. On May 11 vaginal incision and drainage were done. On May 15 an abscess of the right vaginal vault was incised and thick, creamy pus was evacuated. May 18 the patient was transfused. She still had a septic temperature, was drowsy, weak and delirious. Blood culture on May 27 showed a *Streptococcus hemolyticus* infection present. Vaginal examination showed no masses in the pelvis. Two days later, the patient died from a septic bronchopneumonia.

I am now preparing a report on the findings six weeks to five years after operation. Most of the patients volunteered the information that

their general health was much improved and that conjugal relations were much more satisfactory since their operations.

CONCLUSIONS

After ten years of experience, with over 1000 cases operated upon at Mt. Sinai Hospital of Cleveland, the following conclusions may be drawn.

1. The obstetric case should be given the same consideration as major surgery.
2. The presence of lochia, edema, and operative deliveries are not contraindications, neither do they interfere with the performance and results of the repairs.
3. Most of these women leave the hospital in better physical condition and are able to resume their domestic obligations with renewed vigor and vitality.

REFERENCES

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7016 EUCLID AVENUE.

(For discussion, see page 131.)

THE OLSHAUSEN OPERATION FOR RETROVERSION OF THE UTERUS*

A COMPARATIVE STUDY OF ANATOMIC END-RESULTS

By DAVID NYE BARROWS, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Gynecological Department of the New York University and Bellevue Hospital Medical College)

IN REVIEWING the results of operations for retroversion of the uterus performed in the Gynecologic Service of Bellevue Hospital, it was found that the method described many years ago by Olshausen had been employed more frequently than any other during the past seven years.

This has been only one of a number of types of operation in use there for this purpose during this time, and no one of the eight operators has confined himself to any single type of procedure, all varying the methods employed according to the case in hand.

To better gauge these results, a comparison has been made with those cases in which two other standard and popular procedures have been employed, namely, the Simpson-Montgomery and the Webster-

*Read (by invitation) at a meeting of the New York Obstetrical Society, December 13, 1927.

Baldy. These two were selected as they proved to be the next most frequently recorded for this period.

No set rules have existed regulating the choice of operation, but in general the Webster-Baldy was employed where additional ovarian support was required or the abdominal wall afforded poor support, the Olshausen where it was desired to draw the fundus near some particular level on the abdominal wall, and the latter or the Simpson-Montgomery where the ligaments seemed particularly slender near the distal end. In cases where speed was an important factor, to finish a prolonged procedure, the Olshausen operation was frequently used. However, we never use it with a flabby abdominal wall as it is absolutely essential to attach the ligaments to a firm point. If not, the displacement may recur as the abdominal wall sags without any weakness in the ligamentous attachment.

The chief protagonist of the Olshausen operation in this country is Graves, who has used it for about twelve years with complete satisfaction, and who reports practically perfect results with little or no morbidity. His follow-up on 746 out of 1370 cases showed but six failures at examinations made from two months to eight years after operation; three occurred postpartum, two on the cervical stump in prolapse, and one on a case which had suffered a recurrence after a previous operation for retrodisplacement.

Whereas our preliminary investigations did not reveal results as good as he describes, we agree with his pronouncement that it is the simplest and most rapidly performed of all operations now in use for reposition of the uterus, and that its permanence may be compared favorably with other popular procedures.

Its obvious simplicity, eliminating as it does delay due to more or less protracted anatomic dissections, makes it extremely useful as a component part of a prolonged operation, and the absence of injury to surrounding tissues, with accompanying hematomas, trauma, etc., decreases the ensuing morbidity. We also find it extremely useful as an aid in the cure of cystocele.

The frequently mentioned danger of intestinal obstruction and of dystocia must be inappreciable. We have seen none, nor has Graves. The one serious drawback, the silk ligature, it seems universally agreed, is absolutely essential for a successful result. He reported fifteen cases where one silk stitch became infected, requiring removal in only six cases. In seven of our series of 571, which behaved similarly, the silk was removed in only one, several others undoubtedly having the silk slough unobserved.

However, in three cases undergoing a subsequent laparotomy, one ligament has been found to have pulled away from the abdominal

wall and to be attached to the wall merely by a slender cord of peritoneum, 3 to 8 cm. in length.

Our technic is practically identical with that described in the textbooks. Grasping the round ligament gently with an artery forcep to traumatise merely the peritoneum at a point from one to two centimeters from the uterine attachment, the entire thickness of the ligament is picked up on a round curved needle, threaded with number seven braided silk (double). Each stitch is then passed out through the peritoneum, muscle, and aponeurosis at points two or three centimeters to either side of the midline, and after embracing a small bite of these structures, is passed back through the abdominal wall to a point less than one centimeter from its point of exit. Each double ligature is then tied tight, fastening the ligaments snugly against the parietal peritoneum, the knots within the abdomen, and the ends are then cut short. By using the braided silk ligature doubled, one is able by tension in tying the knot to cause sufficient application of the round ligament to the solid structures of the abdominal wall without serious trauma to the ligament or danger of cutting through its muscular tissue. This matter of not tying the suture tight enough to cut through the structures of the ligament early or late, we consider of great importance and believe we avoid many failures for this reason. The distance from the symphysis pubis of this stitch is varied to accord with the inclination desired for the fundus uteri.

In three cases, at subsequent laparotomy done from eighteen months to two and a half years after the Olshausen, no silk has been found.

To compare our results, we have collected 109 out of 135 Webster-Baldy operations and 164 out of 211 in which the procedure described by Simpson and Montgomery was used, as these were done by the same operators who performed the Olshausen operations.

In figuring the percentages, we have classed as failures all cases reported as "fair," "retrocessed," and all degrees of retroversion, to make the statistics as exact as possible. Pain at the site of ligature, so frequently noted in other types of fixation of the round ligament to the abdominal wall, we have found practically nonexistent.

We feel that the grade of intelligence and the social position of our patients probably rank as low as any in the country, so that the presumable amount of postabortal and postpartum care is minimal, and that their convalescent care is practically nonexistent. For that reason, these cases ought to test the efficacy of the operations to the utmost. Under better supervision, many of the poor results would undoubtedly have proved avoidable.

TABLE I. THE RESULTS OF THE WEBSTER-BALDY OPERATION, JAN. 1, 1919 TO JAN 1, 1927

(109 followed up out of 135 done)

POSTOP.	UP TO 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.
Excellent Position	51	27	5	13
Fair	4	0	0	0
Retrocessed	1	1	0	1
Retroverted	3	3	0	0
Excellent—88%				

TABLE II. THE RESULTS OF THE MONTGOMERY-SIMPSON OPERATION, JAN. 1, 1919 TO JAN. 1, 1927

(164 followed up out of 211 done)

POSTOP.	UP TO 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.
Excellent Position	86	35	11	23
Fair	3	1	1	0
Retrocessed	1	0	1	0
Retroverted	1	3	0	0
Excellent—93%				

TABLE III. OLSHAUSEN OPERATION, JAN. 1, 1919 TO JAN. 1, 1927

(432 followed up out of 571 done)

POSTOP.	UP TO 1 YR.	1-3 YR.	3-5 YR.	5-7 YR.
Excellent Position	321	52	23	5
Fair	10	5	0	1
Retrocessed	4	0	2	0
Retroverted	7	4	1	0
Excellent—92%				

The percentage of 92 excellent anatomic results compares favorably with the Webster-Baldy, 88 per cent and the Montgomery-Simpson 93 per cent.

TABLE V. OTHER PROCEDURES ACCOMPANYING RETROVERSION OPERATION

	MONTGOMERY-SIMPSON (211)	WEBSTER-BALDY (135)	OLSHAUSEN (571)
Anterior Colporrhaphy			
Perineorrhaphy			
Cervical Repair	19	13	35
Perineorrhaphy			
Cervical Repair			
Appendectomy	39	33	73
Perineorrhaphy			
Cervical Repair	3	3	0
Perineorrhaphy			
Appendectomy	30	5	26

TABLE VI. OTHER PROCEDURES ACCOMPANYING RETROVERSION OPERATION

	MONTGOMERY-SIMPSON (211)	WEBSTER-BALDY (135)	OLSHAUSEN (571)
Cervical Repair			
Appendectomy	13	12	92
Operation on tube or ovary			
Appendectomy	19	17	112
Appendectomy	29	12	61
Insertion of stem pessary	0	1	7
Uterosacral ligaments shortened	12	2	10

In very few cases (about 16) was the retroversion operation the only procedure done. We have found it extremely useful in helping to support a cystocele case, and also as the final step in a difficult adnexal case, when we wish to prevent adhesions forming with the uterus in retroversion.

TABLE VII. EFFECT OF PREGNANCY

	WEBSTER-BALDY	MONTGOMERY-SIMPSON	OLSHAUSEN
Good after abortion	7	3	3
Good after delivery at term	5	6	10
Poor after abortion	1	0	3
Poor after delivery at term	0	0	0
Percentage good	92%	100%	81%

Unfortunately, many of our cases are delivered under conditions where it is not possible to get any postpartum care or a record of the findings.

It is possible that the cases that have Webster-Baldy and Montgomery-Simpson operations need less postabortal and postpartum care than the Olshausen's, but unfortunately our statistics do not cover enough cases to prove it. The averages, however, are approximately the same.

TABLE VIII. COMPLICATIONS WITH OLSHAUSEN OPERATION IN 571 CASES, JAN. 1, 1919 TO JAN. 1, 1927

Infected wounds	7
Silk removed	1
One round ligament pulled away from abdominal wall	3
Sinus in abdominal incision (4½ yr.)	1
Potential hernia near site of knot	2

So far, the only complications that have been noted are listed here. The cases where the ligaments pulled away were some of the earlier ones, and at that time we were in the habit of tying the silk extremely tight. This, we now feel, may impair the muscular structures of the round ligament to such an extent that the peritoneum is the sole remaining support, and for that reason we now attempt to avoid crushing the ligament by clamp or tie.

The case with the sinus has had an old syphilitic infection of a very obstinate type, which was neglected for a number of years after infection. She has recently been operated upon but has not reported since operation.

The potential herniae were rather wide relaxed areas in the aponeurosis and rather indicated that too wide a bite of this structure had been embraced by the silk ligature.

Of those cases with potential or actual prolapsus, necessitating repair of anterior vaginal wall, perineum or both, 91 had Simpson-Montgomery which is 55 per cent, 54 or 49 per cent had Webster-Baldy, and 132 or 30 per cent had the Olshausen operation performed. Seven in the last named group and one in the first had a stem pessary inserted for dysmenorrhea and an old complete laceration of the perineum was repaired in two cases. This latter we have since ceased to do with any coincident procedure.

In one case in which a Webster-Baldy was not satisfactory, an Olshausen was done at the same sitting. In another which failed after ten months, a Simpson-Montgomery was done at a subsequent operation.

Of these cases of Olshausen operations only one was done on the stump of the cervix after hysterectomy, a procedure which has proved very useful in other clinics.

SUMMARY AND CONCLUSIONS

1. Our results with the Olshausen operation compare favorably with those we have obtained with the Webster-Baldy and Simpson-Montgomery procedures.
2. Pregnancy, whether terminating at full term or prematurely, has proved there is little choice between the three methods.
3. Intestinal obstruction following the Olshausen operation is rare.
4. The silk ligature seldom causes trouble.
5. The ease and rapidity of accomplishment recommend the Olshausen operation, as well as the absence of unnecessary trauma to adjacent structures.

130 EAST FIFTY-SIXTH STREET.

(For discussion, see page 123.)

FETAL MORTALITIES*

AN ANALYTICAL STUDY BASED ON TWO YEARS' RECORDS (1925-1926) AT
HARPER HOSPITAL

BY GEORGE KAMPERMAN, M.D., F.A.C.S., DETROIT, MICH.

FETAL mortality is an all absorbing topic to the obstetrician, and because of this realization we believe that the record of the fetal mortalities at Harper Hospital during 1925 and 1926 will be of some interest to the members of this society. It is not our aim to pare down our mortality figures by deducting certain cases for which no one need share responsibility. In fact we aim not simply to consider deaths for which an individual may be responsible, but would rather consider fetal deaths as they actually occur and if possible by analysis to show where there is opportunity for improvement. We wish to present to you the work of the hospital group, with our results. We frankly offer you the facts, and we invite your cooperation by your criticism, analysis, and discussion.*

This record of fetal deaths includes all deaths of the fetus that occurred during the maternal stay in the hospital. As all pregnancies of five or more months are cared for in the obstetric division, the fetal deaths include many very premature fetuses. During these two years the total births numbered 2478, and 163 fetal deaths are recorded, a fetal mortality of 6.65 per cent. But this record includes no

*Read at a meeting of the Detroit Obstetrical and Gynecological Society, February 7, 1927.

cases prior to five months. If one could estimate the number of miscarriages that occur before five months, it would then show us the appalling number of fetal deaths that really do occur. Such figures would be mere conjecture on our part, yet it is easy to infer that the actual loss of fetal life is far greater than the mortality percentage as shown in any hospital report.

In trying to analyze the causes of fetal death we have grouped the cases in three major groups: (1) Fetal death before viability; (2) Borderline cases, or in other words, premature infants which although premature had a prospect of surviving; (3) Full term, or practically full-term infants.

We would like to interject just a word here as to what constitutes viability, as interpreted in this series. After a careful study of each record a fetus that was frankly not of seven months development and did not weigh 1500 grams or $3\frac{1}{8}$ pounds was considered as nonviable. We believe that weight is not the only criterion, as a full-term baby of small weight does not present as great a problem as a premature baby of the same weight.

FETAL DEATHS PRIOR TO VIABILITY

Among these 2478 births there are recorded 63 deaths of nonviable fetus, a mortality in this group of 2.54 per cent. The tabulated matter (Group I) shows the classification of the causes of these deaths.

GROUP I	
Nephritic toxemia	22
Unknown	24
Placental bleeding	7
Congenital malformations	3
Maternal toxemia, not nephritic or eclamptic	2
Maternal cardiac decompensation	1
Maternal overexertion	1
Previous amputation of cervix	1
Maternal pneumonia	1
Syphilis	1
Total	63 -2.54 per cent of entire series.

On reviewing this group it will be seen that in about one-third of these cases the cause of death is unknown. These 24 cases of unknown fetal death include eight twins (4 pairs). In these cases no maternal cause for the early onset of labor could be found. By this we mean that these mothers had normal urines, normal blood pressures, negative Wassermanns, and were apparently free from any physical condition which is known to be a factor in causing premature labor. Since intrinsic disease of the ovum is recognized as a possible cause of miscarriage, it is possible that some of these might fall in that group. Probably some were syphilitic; but that is mere conjecture which can neither be proved nor disproved.

The most common known cause of fetal death at this series is nephritic toxemia. Twenty-two cases are classified under this heading, about one-third of the entire series of deaths of nonviable fetus. This large proportion of cases emphasizes the importance of nephritis as a cause of fetal death. In a rather large percentage of these cases the mother had been in the hospital under observation and treatment for some time before the fetal death occurred. In this group the number of stillbirths was about equal in frequency to those that survived a short time. About one-half of the stillbirths were macerated, or one-fourth of all those that died because of maternal nephritis.

Seven fetal deaths in this series were associated with placental hemorrhage. A careful analysis of these seven cases would lead us to list four of these as being placenta previa, and three as abruptio placentae. In all these cases bleeding had been a prominent symptom for considerable time before the fetal birth. In two of the cases of placenta previa the premature birth was perhaps definitely precipitated by the insertion of a bag to control the bleeding.

Three fetal deaths are ascribed to fetal malformation. These were cases of acrania with spina bifida.

Two fetal deaths occurred because of maternal toxemia other than nephritis. One of these was a general septicemia of unknown origin and the other was an unusual case of toxic vomiting of pregnancy.

We realize that the incidence of these conditions is peculiar to this small series. This is particularly emphasized by the recording of only one case of fetal death from syphilis in the entire series.

FETAL DEATHS AMONG THOSE PREMATURE, BUT VIABLE

This small series represents a few borderline cases which, although premature, had a fair prospect of surviving. This group contains 22 cases, or 0.88 per cent of the entire number of births during the two years. Group II will show the classification of the cases in this series.

GROUP II

Nephritic toxemia	6
Unknown	5
Placental bleeding	5
Eclampsia	2
Fetal malformation	2
Toxic vomiting	1
Accidental rupture of membranes	1
Total	22 cases 0.88 per cent of entire series

In this series it will be noted that in five instances the cause of the premature labor was unknown, or in about one-fourth of this series. The largest number of premature births is again ascribed to nephritis, six out of twenty-two. Of these six, one was born macerated. Four were born alive and lived a very short time.

Placental bleeding was the cause of fetal death in 5 cases of this series. Two of these were considered placenta previa, and three were cases of abruptio placentae.

Eclampsia was the cause of fetal death in two of these prematures. In one case the patient had several convulsions while the other was a preeclamptic toxemia.

DEATHS AMONG PREMATURES

3.59 per cent of entire series

COMBINATION OF GROUPS I AND II

Nephritic Toxemia	28
Unknown	29
Placental bleeding	12
Malformations	5
Eclampsia	2
Other Toxemias	2
Toxic vomiting	1
Rupture of membranes	1
Cardiac disease	1
Overexertion	1
Previous amputation of cervix	1
Pneumonia	1
Syphilis	1
Total	85 cases

If now we combine Groups I and II as above, we find that in both groups nephritic toxemia is the largest known factor in producing fetal deaths in this series, 28 fetal deaths among 85, a total of 33 per cent. Also it will be noted that placental bleeding is the second largest known factor in both groups, 12 fetal deaths among the 85 prematures, a mortality of 14 per cent. Also the 85 deaths in prematures represent a fetal mortality of 3.59 per cent, over half of the total fetal mortality in the entire series of 2478 births.

FETAL DEATHS AT FULL TERM

In this third group of cases we list all cases at full term or in the last month of pregnancy. The fetal deaths in this group number 78, a mortality of 3.14 per cent. This group represents about one-half of the fetal mortalities in the entire series. These are all babies that should have had a chance for life, at least as far as their size and period of development was concerned, and the analysis of this group in particular should show us where our obstetric work is probably insufficient. These cases may be classified as Group III.

GROUP III

1. Associated with labor and delivery	44
a. Delivery deaths (30 cases)	
Forceps delivery	8
Forceps and version	4
Version	4
Breech extraction	2

Spontaneous labor		
cerebral hemorrhage	6	
cause unknown	3	
Forcep delivery for failing fetal heart	3	
b. Hemorrhage during labor	6	
c. Prolapse of cord	5	
d. Transverse position	1	
e. Face presentation	1	
f. Eclampsia	1	
2. Malformations		13
a. Hydrocephalus with spina bifida	3	
b. Hydrocephalus	2	
c. Atresia of esophagus	1	
d. Atresia of ilium	1	
e. Atresia of bile ducts	1	
f. Brain defect, absence of lobe	1	
g. Congenital goiter	1	
h. Congenital heart, death not at delivery	2	
i. Teratoma of sacrum with spina bifida	1	
3. Nephritic Toxemia		5
4. Intrauterine death prior to labor, cause unknown		4
5. Unknown (atelectasis?)		1
6. Adrenal hemorrhage		1
7. Neonatal mortality		6
a. Melena neonatorum	3	
b. Suppurative stomatitis	1	
c. Enlarged thymus	1	
d. Erysipelas	1	
8. Postmaturity		4
Total		78

The most important group here to be considered are those fetal deaths associated with labor or delivery. But before discussing this group, we would like to review briefly the other causes of death in this series and then have all the remaining time for the important group of delivery deaths.

Malformations are credited with thirteen fetal deaths. This group represents the cases that had a gross defect which was incompatible with life. A few cases of congenital heart disease could properly be included here, but they are classified with the labor deaths because death occurred during labor or immediately after delivery, the autopsy showing the cause of death. These gross malformations represent 16 per cent of all deaths at full term and obviously it would be impossible to influence this mortality in any way. They are of interest chiefly in the explanation of their occurrence and not from the prophylactic standpoint. These malformations can be classified as follows:

Hydrocephalus with spina bifida	3 cases
Hydrocephalus	2
Atresia of esophagus	1
Atresia of ileum	1
Atresia of bile ducts	1
Brain defect, absence of lobe	1
Congenital goiter	1
Congenital heart	2
(Death not at delivery)	
Teratoma of sacrum with spina bifida	1
Total	13 cases

Nephritic toxemia in this group is represented by 5 fetal deaths, a percentage of 6.4 of the full-term fetal deaths. These are not labor deaths, but occurred before the onset of labor. Deaths among nephritics occurring during labor and delivery will be classified elsewhere.

Among these full-term deaths are four fetal deaths occurring intra-uterine without any known cause. In these cases no maternal or fetal cause was ever found. These deaths all occurred before onset of labor and fetal death was definitely diagnosed in each case.

One postnatal death is classified as from unknown cause. From the clinical record one could perhaps call it an atelectasis, but this could not be given as a positive diagnosis.

One death is recorded as being due to adrenal hemorrhage. This was a postnatal death occurring three days after delivery. During labor the fetal heart had been somewhat alarmingly irregular and a low forcep delivery was performed because of the cardiac irregularity. The delivery was easy and the baby seemed vigorous and normal and nursed well. On the third day the baby's condition suddenly changed and the baby appeared to be in collapse. Autopsy showed a normal heart. The adrenals were hemorrhagic in appearance, and in the opinion of the pathologist were the cause of death. The cause of adrenal hemorrhage is unknown. The autopsy showed no other cause of death.

This series shows six neonatal deaths. The causes of death are given as follows:

Melena neonatorum	3 cases
Enlarged thymus	1
Erysipelas	1
Suppurative stomatitis	1

The suppurative stomatitis occurred in a baby born easily and spontaneously and first began on the seventh day postpartum. This began with a swelling of jaw and neck, associated with fever. The infection spread to the mediastinum and was fatal in two days. The attending pediatrician was of the opinion that the baby had been infected by the breast milk. Extensive cultures of breast milk showed only staphylococcus, while the baby's infection was a streptococcus. The mother was given an extensive examination for focal infections. She had a mild streptococcus tonsil infection and since her delivery her tonsils have been removed in the hope of preventing another such fetal death. This patient has two living children.

The four deaths ascribed to postmaturity were four cases that apparently went about a month beyond the estimated date and in these cases fetal death occurred before the onset of labor. No other cause of the fetal deaths could be found, and they are classified as being due to postmaturity. In a personal communication from Dr. DeLee he states that he considers postmaturity as a definite cause of fetal death.

Usually, however, it is my habit not to take going beyond the estimated date as anything very serious and, as a rule, wait for labor to start spontaneously regardless of the number of days overdue.*

SUMMARY

CAUSES OF FETAL DEATHS IN ENTIRE SERIES. 2478 BIRTHS, 163 DEATHS,
6.65 PER CENT

	NONVIABLE	PREMATURE	FULL TERM	TOTAL	PER CENT
Unknown	24	5	8	37	22.7
Nephritic toxemia	22	6	5	33	20.2
Placental bleeding	7	5	6	18	11.0
Malformations	3	2	13	18	11.0
Delivery deaths			18	18	11.0
Labor deaths			11	11	6.7
Prolapse of cord			5	5	3.0
Neonatal deaths			6	6	3.6
Postmaturity			4	4	2.4
Adrenal hemorrhage			1	1	0.6
Eclampsia		2	1	3	1.8
Toxic vomiting		1		1	0.6
Accidental rupture of membranes		1		1	0.6
Toxemia, unclassified	2			2	1.2
Cardiac decompensation	1			1	0.6
Overexertion	1			1	0.6
Amputation of cervix	1			1	0.6
Pneumonia	1			1	0.6
Syphilis	1			1	0.6
Total				163	

1807 DAVID WHITNEY BUILDING.

*The detailed case histories will be found in the author's reprints.

THE PRESENT STATUS OF THE ERGOT QUESTION, WITH
PARTICULAR REFERENCE TO THE PREPARATIONS
USED IN OBSTETRICS AND GYNECOLOGY

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RECENT work bearing on the composition of ergot and the action of the substances therein present makes a consideration of the preparations of this drug upon the American market, and their use, of considerable importance.

According to current views there are present in ergot, two groups of active substances: the alkaloids, crystalline ergotinine (1), amorphous ergotinine, otherwise known as ergotoxine (2) or hydroergotinine (3), ergotamine and its isomer ergotaminine (4); and the amines, of which histamine and tyramine only seem to be of particular importance from either the pharmacologic or the clinical standpoint.

Ergotinine has been found to be a relatively inactive substance, the early reports ascribing to it considerable activity, not all, as pointed out by Barger and Dales⁵ being based on the use of pure specimens of the alkaloid. Kobert⁶ using a pure specimen found it almost entirely without activity, and more recent reports show that while it does have some pharmacodynamic properties these are relatively weak as compared with the other active materials. For example it has about one three-hundredth the strength of ergotamine judged by its action in paralyzing the renal vasomotors⁸ and about one five-hundredth the stimulant action of the same drug upon the isolated guinea pig uterus.^{7,4} Ergotoxine, as the amorphous ergotinine is best known, has a much more marked activity. Among its pharmacologic actions are those of producing the characteristic bluing and gangrene of the cock's comb, the stimulation of the excised uterus (rat, cat, guinea pig) as well as that in situ (cat, rabbit, monkey), and the well-known vasomotor reversal, due to paralysis of the motor sympathetic fibers.⁹ Of the other alkaloids, the only statement regarding ergotaminine seems to be that of Spiro⁴ that it falls between histamine and ergotamine in its action in the excised uterus, having more effect on the tone than the frequency of contractions, and that it is relatively nontoxic, 3 milligrams having been without effect on a 440 gram guinea pig.

Since the isolation of ergotamine an extensive literature has appeared both on its pharmacology and its clinical use.¹⁰ Although it is clearly different in its physical and chemical properties from ergotoxine, the two substances seem closely allied as to their pharmacodynamic activity. Dale and Spiro¹¹ stated that qualitatively they were equal and the quantitative differences were slight, so that for practical purposes the two substances might be said to be the same. Although further work has not altogether confirmed this view, the differences are of academic rather than clinical importance at this time. The most important action ergotamine

*Associate Professor and Upjohn Fellow in Pharmacology, respectively.

possesses from the standpoint of its use is that of stimulating both tone and contractions of the uterus. For example, the excised uterus of the virgin guinea pig is stimulated when the alkaloid is present in the surrounding bath in a concentration of 1:125,000,000.¹¹ The isolated uteri of the rat and cat and that of the rabbit *in situ* also are stimulated. Small doses may be repeated, while after one large dose, further administration is ineffective. The contraction of the excised uterus is not so prompt as that from histamine, but is more persistent, and it is more difficult to restore the uterus to its previous state of activity by washing out the drug than is the case after histamine.

Of the amines present only two have activity sufficient or have been shown to be present in amounts adequate to possess any important share in the action of ergot on the uterus. These are tyramine and histamine, which are in no sense specific to this drug. Indeed it has not been established that they occur in perfectly fresh crude ergot and according to Spiro and Stoll⁴ their presence is inconstant. They are, however, usually present in the galenical preparations, and the pharmacologic activity of these preparations may be due to them to a considerable degree. Broom and Clark¹⁴ have shown for example, that the action of the B. P. Liquid Extract is due almost entirely to the amines present, and the U. S. P. Fluid Extract seemed to have about equal amounts (judged by activity) of the two groups, alkaloids and amines. Forst and Weese¹³ found in different preparations of ergot, that histamine was present in quantities varying from traces up to 0.4 mg. per cubic centimeter of finished product.

The relative activity of these two substances is very different. Tyramine causes a rise in blood pressure, histamine a fall (in carnivorous animals and man). Tyramine has less than one two-hundredth the activity of histamine on the excised uterus. Though no statement of the relative amounts of the two substances present in ergot preparations is available, it is usually accepted that more activity may be ascribed to the histamine present than to the tyramine.

The task of evaluating clinical reports on the merits of ergot as such or of any of its constituents is difficult for several reasons. Ergot varies in strength as collected and then may lose a part of its activity before being prepared for use. The preparations when made do not necessarily contain the active materials. In general, preparations made by use of water as an extracting agent contain chiefly amines, while preparations made by a method using acid-alcohol, such as that outlined by the U. S. P. for the fluid extract, are rich in alkaloids, provided of course that these were present in the crude drug in sufficient amount. This difference in preparations was noted long ago by Barger and Dale⁵ and Cushny¹⁴ and recently verified by Broom and Clark¹² while further confirmation is offered in the present paper. A negative clinical result may be due to the use of an inactive preparation. Finally it is very difficult for the obstetrician to say that adequate and maintained contraction of the uterus following delivery is due to the activity of a drug, or drugs, he may have given or to the natural tendency of the uterine muscle itself.

Not a great deal has been written about the clinical action of the ergot preparations (other than the individual constituents) in recent years, but if one may judge by the statements in the standard textbooks of obstetrics or gynecology, it is used in this country chiefly to prevent postpartum hemorrhage, or to contract atonic uteri after delivery. To a lesser extent it seems to be used against various types of bleeding of gynecologic origin, such as that from myomas of the uterus. Practically all American authorities deprecate strongly its use during labor, or before the delivery of the placenta. The use to

prevent hemorrhage after abortion or curettage is entirely analogous from the standpoint of mechanism to its use to prevent postpartum hemorrhage. The use during the puerperal period, to hasten involution, is somewhat different, and in the light of the work of Bourne and Burn (cited below) perhaps not so important as usually considered. In the discussion of the use of ergot in textbooks no recognition of a possible difference in action of the different preparations has been made. In the literature here discussed, only reports in which it has been possible to determine the type of preparation used have been included.

Although ergotoxine was for some considerable time available for medical use, very few reports on its action have appeared. Sharp¹⁵ found its action when injected similar to that of ergot, more prompt but more evanescent. Kehrer¹⁶ found that injection of 1 to 2 milligrams was ineffective. In 1923 the statement was made in the British Codex that "Ergotoxine has been used clinically for its action on the uterus, but it is disappointing, and gynecologists are now generally agreed that it is not the active constituent of ergot they want."

The shortage and high cost of ergot during and after the war led in Europe to many attempts at using synthetic ergot substitutes, chiefly histamine, tyramine or both in combination. Using tyramine alone, Heimann and Abel found it a complete substitute for ergot, without the toxicity of the latter.¹⁸ Sharp,¹⁵ Kehrer¹⁶ and Bourne and Burn¹⁷ obtained only negative results from its use. Barbour's¹⁹ successful results were obtained with quantities very much larger than occur in therapeutic doses of ergot.

Histamine alone was tried by Koch,²⁰ Jäger,²¹ Kehrer¹⁶ and Bourne and Burn.¹⁷ The first author used one milligram hypodermically, during labor, and found that it stimulated the pains when they were weak. Jäger obtained similar results, if adequate doses were given (8 mg. injected), but noted unpleasant side effects, flushing, erythema, and headache. Kehrer (1 to 2 mg. injected) did not confirm the finding of uterine stimulation, recording the contractions graphically by means of a balloon in the uterine cavity connected to a manometer, but saw even more marked symptoms, including respiratory disturbances and clonic spasms.

More frequently than either of the amines alone, there was used a mixture of the two, usually containing 0.000,125 gm. histamine and 0.0065 gm. tyramine.²¹ Inasmuch as it has been shown that the strength of histamine is some five to fifteen hundred times greater on the isolated uterus than that of tyramine,²² the probabilities are that in this preparation in which the amount of tyramine is only fifty times that of the histamine, the activity is almost wholly due to the histamine. Jäger gave this preparation to 250 patients for the pre-

vention of postpartum hemorrhage, with eight failures. He lists 150 additional cases from the literature, with ten failures. It was also used to prevent hemorrhage following spontaneous or instrumental abortion. Kosminski²¹ and Jäger also found it of some value in the treatment of bleeding from gynecologic causes, as from myomas of the uterus. The drug was always administered by subcutaneous or intramuscular injection, a warning being given against its intravenous administration. Rübsamen, Wasicky, Hoffmann,²³ however, found the action too fleeting to be of value.

A consideration, aside from the negative clinical results, making one disinclined to ascribe to histamine or tyramine any important share in the action of ergot, is the evidence from a number of sources that these amines are not active when taken by mouth, whereas ergot will produce its effects irrespective of the route of administration.

While the literature of the use of ergotoxine is very limited (*vide supra*), since the isolation of ergotamine in 1922 a large number of papers have appeared dealing with its use, chiefly to prevent or control postpartum hemorrhage from atonic uteri.²⁴ Other indications are retained lochia, delayed involution, prevention of bleeding in cesarean section, treatment of bleeding from abortion, either spontaneous or following instrumental emptying of the uterus. In the treatment of incomplete abortion with retention of placental rests, only Turol reports good results. In general all authors speak strongly against its use during labor, as a number of cases of tetanic contraction of the uterus, with asphyxia of the child, have occurred following this use. Schnitzer²⁶ speaks especially strongly against this practice, even with the use of small doses, and holds that the manufacturer should indicate on the container that it is not to be used in this way. Kopischke²⁷ and Turol²⁵ failed to induce abortion with ergotamine. Hellmann²⁸ found that ergotamine facilitated curettage by rendering the uterus firm. Although Wetterwald²⁹ gave single doses of 0.5 milligram intravenously (with unpleasant symptoms in 30 per cent of his cases), practically all writers have given it either intramuscularly or subcutaneously, or during the puerperium or for gynecologic bleeding, by mouth. The unpleasant side effects are most often seen in gynecologic practice, during the puerperal period, or when given after instrumental abortion. These are reported as occurring in varying degree, depending in part on the dose and route of administration, and in part it is said on the stability of the nervous system of the individual. Nausea and vomiting, persistent headaches, cyanosis, muscle pains, and rarely collapse have been observed. For some unexplained reason, when given postpartum, other symptoms are rarely noted. Kopischke²⁷ advises against its use in ambulatory patients, confining it to hospital practice, and in this, Lützenkirchen³⁰ concurs. The gynecologic uses are not so clear-cut as those following childbirth. It has

been recommended for metrorrhagia of various forms, climacteric, from myomas, etc. For this use it has been given orally. Such use must be carefully guarded, as Panter³¹ has reported a case of production of a tabetic condition after five milligrams in three days, and Carreras³² a fatal case of gangrene of the feet after a total of approximately four milligrams, orally, through one week.

Recently Bourne and Burn¹⁷ in a short series of experiments have examined the action of histamine, tyramine, and ergotamine intrapartum, recording the uterine contractions by means of a balloon in the uterine cavity attached to a recording manometer. Tyramine (10 mg.) injected produced only a single contraction. Histamine (2 mg.) produced a powerful but short-lived stimulation, followed apparently by uterine exhaustion. Ergotamine, however (1 mg. injected), produced a powerful contraction of the uterus, lasting sixteen hours. Such an action of course would contraindicate its use during labor, but would make it of considerable value to maintain uterine contraction after delivery of the placenta.

Bourne and Burn also carried out another experiment which throws some interesting light on the use of ergot preparations during the puerperium. Three preparations were administered to a series of normal patients during the puerperium. Of these one was an ergot preparation known to be rich in the active alkaloids, one a practically inert preparation of ergot and the third a preparation of inert substances made up to resemble the other two. Two of these were administered to two series of twelve patients each, and the third to a series of eight. Observations were made daily as to the height of the uterus above the symphysis, and the color and amount of the lochial discharge. At the end of the week it was impossible to tell which patients had received the active ergot and which either of the other materials. Such results make one suspicious of all claims made for the value of any type of ergot preparation during the puerperium, but of course have no bearing on the action postpartum.

The literature on the use of ergotamine has been discussed in detail, because here for the first time is a substance which seems to have all of the effects which are usually held to be characteristic of ergot. On the other hand the evidence for the value of tyramine and ergotoxine in obstetrics or gynecology is lacking, and that for histamine is questionable. Whether or not these four substances represent the entire activity of ergot is not yet established. Halphen³³ believes that they do not. At any rate, of the substances thus far isolated, ergotamine seems to have had the most extensive clinical trial, and apparently will do all that ergot will do.

If this be correct, then it becomes pertinent to reexamine the preparations of ergot which are available to the physician. The pharmacologist and chemist seem to be in agreement as to the active constitu-

ents of ergot, and such clinical results as are available offer corroboration of their view. Then it should be made certain that preparations containing the active materials are available, and only such preparations should be used in the practice of medicine.

In order to throw some light on the relative strength of the ergot preparations now available, a number have been assayed by two biologic methods, no chemical method being available. The U. S. P. X. requires that the official fluid extract shall possess the same activity as an equal amount of the standard fluid extract furnished by the Bureau of Chemistry of the U. S. Department of Agriculture, when tested by the cock's-comb method.

This method in brief consists in determining the amount of the fluid extract being assayed necessary to produce the same degree of bluing of the comb of susceptible white Leghorn cocks as is produced by a standard dose of the standard fluid extract. Details of the method are given in the U. S. P. X. and in the papers of Edmunds and Hale, Gittinger and Munch, and others.³⁴ This method measures the alkaloids present. It may seem a legitimate question from the clinical standpoint to ask how far such a test actually can measure the therapeutic efficiency of a drug in action upon the human uterus. This, of course, it does not do, but does measure as well as any available method (with the possible exception of the other used in this study) the concentration or amount of the substances to which the therapeutic action is believed to be due. The evidence on this point is clear, for the amines do not produce the characteristic effects on roosters,³⁵ while the alkaloids not only have this effect but will, if given in large or repeated doses, bring about gangrene of the comb and wattles.^{5, 11, 12} Gangrene may also be produced in the tail of the white rat³⁶ and in one case has been seen in the human extremities, similar to that occurring in chronic ergot poisoning.³²

The U. S. P. X. method and another recently described have been used in making the assays, the results of which are noted below. The second method is that of Broom and Clark,¹² which also measures the alkaloidal content of ergot. This method as slightly modified consists in suspending two similar strips of the uterus of a parous, but not pregnant, rabbit in Ringer's solution in two similar chambers, under similar conditions of temperature and oxygen supply. The amount of epinephrine necessary to produce a good contraction of each strip is noted, and then the amount of the ergot preparations being compared necessary to produce the same degree of paralysis in the two strips to subsequent similar applications of epinephrine, is determined. This may require the use of several pairs of strips, but with reasonable familiarity with the technic the method yields fairly accurate comparisons, possibly more accurate, especially in the case of weak preparations, than that of the U. S. P. X.

There are a number of other assay methods, two of which are extensively used in this country, but neither of which have sufficient in their favor to justify their use. One consists in determining the stimulant activity of the preparation on the isolated uterus of the virgin guinea pig. There are a number of substances present in galenic preparations, histamine, tyramine, potassium chloride, acetyl-cholin, as well as the alkaloids, all of which will stimulate the isolated uterus, but of these, histamine is the most active, so that such a test measures chiefly the histamine content. A second method consists in determining the amount of ergot preparation necessary to produce a standard rise in blood pressure. This again measures the composite action of all the materials present, some of which are pressor, while others, as histamine, are markedly depressor. There is no way of evaluating accurately the

part played by any one of the constituents under such circumstances. Yet prior to the appearance of the U. S. P. X. apparently about half the men making ergot assays in this country were using this method.

In the present paper, using the cock's-comb method of the U. S. P. X. and the epinephrine reversal method of Broom and Clark, four types of preparations have been assayed. From different specimens of crude ergot different fluid extracts have been made in the laboratory by the U. S. P. X. method. These have been preserved in 10 c.c. ampules in the refrigerator and were from twelve to eighteen months old at the time of assay. A second group consists of U. S. P. fluid extracts purchased on the open market, some in original containers, others as dispensed from the stocks of the local retail druggists. A third group consists of a number of ampule preparations for administration by injection. These were all products of reputable manufacturers, and in several cases made by the same firms as the fluid extracts. Finally one specimen of the extract "Ergotine Bonjean" was examined, though there was no reason to suppose that any alkaloids would be present in it. Judging by the demands for this material on the retail druggist it is not in very extensive use at present, and only one specimen was assayed.

From examination of the table it will be seen that the fluid extracts, both those made in the laboratory and those purchased from the

TABLE I. SHOWING THE COMPARATIVE STRENGTHS OF A NUMBER OF ERGOT PREPARATIONS, ASSAYED BY TWO METHODS

GROUP	NO.	TYPE OF PREPARATION	ASSAY METHOD	
			U. S. P. X.	BROOM-CLARK
A.	1	Standard fluid extract	100%	100%
B.	2	Laboratory fluid extract	200	190
	3	Laboratory fluid extract	150	175-200
	4	Laboratory fluid extract	100	100
C.	5	Commercial fluid extract	Below 25	5-10
	6	Commercial fluid extract	100	100
	7	Commercial fluid extract	100	100
D.	8	Ampoule preparations	Below 25	Below 6
	9	Ampoule preparations	Below 12	Below 2
	10	Ampoule preparations	—	Below 2
	11	Ampoule preparations	Below 10	Below 3
E.	12	Ergotine Bonjean	Below 25	Below 1

Group A. The standard sent out by the U. S. Bureau of Chemistry. B. Fluid extracts made from crude ergot in the laboratory. C. Commercial fluid extracts. D. Commercial preparations, in sterile ampoules, for injection. E. Ergotine Bonjean, a solid extract.

retail druggist were up to or above the standard set by the U. S. P. Only one fluid extract was not of the required strength, and that though made by a reputable manufacturer, had been open on the shelves of the pharmacy for at least six months. Of the hypodermic preparations none possess any important degree of activity by either method. This finding is very important. It seemed to be the opinion of the retail pharmacist that the ampules are more extensively used

than the official preparations, and yet they seem to be almost wholly devoid of activity. A word with respect to the method of reporting the values in the table should be added. An average susceptible cock reacts with the right degree of bluing of the comb to a dose of 0.5 c.c. of the fluid extract per kilogram. If such a cock received 2.0 c.c. per kilogram of the preparation being assayed, and still did not react, no further injections were made in other cocks and the strength was reported merely as less than 25 per cent, although actually there may have been *no* active material present. From this it follows that there is no discrepancy between a value reported as "below 25 per cent" in the table of values by the U. S. P. method and "below 5 per cent" in the values by the other method. The proper interpretation is that the actual value in each case lies somewhere between zero and the percentage given. When actual values are reported (not preceded in the table by "below"), they are in good agreement.

The conclusions to be drawn from the examination of these preparations seem fairly obvious to us. Much of the dissatisfaction with the results from ergot administration has its explanation in the use of preparations which do not contain the active substances. The method of correction lies in the use of either the U. S. P. official preparation properly made and assayed by responsible manufacturers, or preparations of the alkaloids or known to contain them. It is not so easy to understand why the hypodermic preparations are so extensively used, in view of their apparent inactivity. Perhaps one reason is that there are often administered with the ergot, hypodermic preparations of pituitary, which as has been shown elsewhere, are both active and stable. If the action of ergot is desired, preparations should be used which have been shown by the proper type of assay to be active.

It should be stated here that we have felt that nothing would be gained by identifying the different preparations assayed. Where a standard exists, the manufacturers seem to have made a serious effort to comply with it, marketing satisfactory preparations, and the physician can best protect his patient and himself by using such standardized official preparations.

SUMMARY

1. The active substances in ergot or its preparations are histamine, tyramine, ergotoxine, and ergotamine.

2. All of these substances will stimulate the isolated uterus, but there is no satisfactory clinical evidence for the value of tyramine or ergotoxine in obstetrics or gynecology; the evidence for histamine is somewhat questionable; adequate clinical as well as experimental evidence exists to justify the conclusion that the alkaloid ergotamine is the most important constituent of ergot, and the one whose presence in ergot preparations should be insured.

3. An examination of a number of the ergot preparations available in the market reveals that only the U. S. P. fluid extracts contain important amounts of the active alkaloids.

4. Only the official fluid extract or preparations definitely shown by proper methods of assay to contain the alkaloids of ergot should be used in medicine.

Acknowledgment.—We desire to acknowledge the generous and unconditional support of The Upjohn Company, of Kalamazoo, Michigan, which has made possible a study of ergot of which this report forms only a part.

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THE RELATION OF GALL BLADDER DISEASE TO PREGNANCY*

WITH SPECIAL RELATION TO THE FACTOR OF HYPERCHOLESTEROLEMIA

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THE relative frequency of gall bladder disease, and of cholelithiasis naturally demands some thought as to its cause and prevention. It holds a place with the more serious of abdominal diseases, and operations for the relief of gallstones are always attended with considerable apprehension on the part of the surgeon, especially when there is an associated jaundice.

The most frequent cause of symptoms in all gall bladder disease is gallstones, and a study of their cause and prevention entails a study of the pathogenesis of gallstone formation. The following thoughts are in relation to that study.

In reviewing any series of cases of cholelithiasis one is impressed with the high occurrence of the disease in females. In a recent series of 136 operated cases,¹ 82 per cent of them were females. The figures given in the literature generally range from 70 per cent to 80 per cent. This high incidence of the disease leads to the question as to what distinctly female function would predispose to gallstone formation. Pregnancy and the menstrual cycle suggest themselves as the most prominent female characteristics, and these functions must be studied with the idea of finding a condition which could predispose to the formation of gallstones, and yet could be paralleled in the male, because cholelithiasis is found in that sex.

The relation of pregnancy to gall bladder disease was first noted by Huchard in 1882. Since that time many writers have confirmed his observation. Osler stated that 90 per cent of women with gallstones have borne children, and Mayo² writes that "90 per cent of married women who have borne children have gallstones, and 90 per cent of these women identify the beginning of symptoms with some particular pregnancy."

In a recent series of 112 female patients with gall bladder disease, 95, or 84.8 per cent, had borne children. Of this group 20 patients definitely dated their first attack as occurring during or within the few months following pregnancy. Seven patients under thirty years of age were married, and in each case their attacks of gallstone colic preceded or followed their first delivery.

*Read at a meeting of the Obstetrical Society of Philadelphia, October 6, 1927.

If, however, we inquire as to the incidence of gall bladder disease in a series of pregnancy cases, we are surprised to find the figures relatively low. In a group of 400 pregnancy cases recorded at the Maternity Clinic at the University Hospital, there were 16 cases who showed symptoms of definite gall bladder disease, an incidence of only 4 per cent. Six other patients had had gall bladder operations previously, all of which postdated pregnancies, making really an incidence of gall bladder disease of 5.5 per cent in 400 pregnancies. The average age of this group was 28.4 years.

For comparison, we subjected a questionnaire to 227 unmarried women, whose average age was 20.7 years. In this group we found:

- 1 gall bladder operation,
- 2 cases with pain in upper right quadrant,
- 4 cases with distention after meals, and
- 1 case with excessive gaseous eructations.

It is hard to evaluate this data, but it is doubtful whether more than 2 or 3 cases could be classed as cases of cholelithiasis.

The stones found in the young women whose gallstones were removed during or following a pregnancy, were small, round, soft, single or multiple, and composed almost entirely of crystalline cholesterol. The gall bladder in these cases was of normal color and texture and without adhesions.

Those removed from older women were larger, faceted, and pigmented, and were usually found in a gall bladder which was greyish-pink in color, thick, and often surrounded by dense adhesions.

These facts suggest the possibility that the stones are formed early in adult life, causing discomfort to the patient only by an occasional temporary obstruction of the cystic duct. As the patient grows older the stones increase in size and number, causing increasing trauma to the gall bladder wall, and inviting infection. By the time the patient reaches the late thirties, the gall bladder is a dense firm functionless organ, full of stones, causing constant disturbances of digestion with frequent attacks of sharp pain. She finally comes to the surgeon for relief of a disease which has really been of ten or fifteen years' duration.

Now let us turn to a study of gallstones themselves, and the relation pregnancy bears to their formation. The calculi have been divided by Mentzer³ into two groups, according to their composition. The cholesterol group, which comprises the large majority of gallstones, includes the pure cholesterol stone; the radiate cholesterol stone, radiating cholesterol stones about a nucleus; and the common stone, mostly cholesterol with varying amounts of bile pigments deposited as salts of various metals.

The other group is of calcium bilirubin stones, which contain very little cholesterol. They are small, black, spicular, multiple, and are found very rarely.

Because cholesterol forms such a large part of the majority of gallstones, Aschoff and Baumeister⁴ suggested some derangement of the body lipid metabolism as one of the chief causes of gallstone formation. They believed that an increase of cholesterol in the blood causes a commensurate increase in cholesterol excretion via the bile. Fasiani⁵ has demonstrated experimentally that an increase in the cholesterol content of the bile follows intravenous injection of cholesterol. D'Amato⁶ in feeding experiments found that foods rich in cholesterol increased the cholesterol of the bile from 6 to 8 mg. daily, and Stepp⁷ fed rats and dogs on a lipid free diet for a number of weeks, and found the biliary cholesterol 10 to 15 per cent lower than the normal at necropsy.

An increase in biliary cholesterol combined with stasis and concentration in the gall bladder are factors, which, according to Aschoff⁸ are sufficient to cause crystallization and precipitation of cholesterol. Stasis in the flow of bile is no doubt produced very frequently during pregnancy by the pressure of the distended uterus on the upper abdominal organs. To these factors has been added a fourth; viz., a change in the reaction of the bile toward the alkaline side, suggested by Lichwitz.⁹ This may well be the part played by bacteria in the bile.

The primary factor, however, in the formation of most gallstones is probably a hypercholesterolemia, with a resultant increase in biliary cholesterol. The two commonest conditions in which the blood cholesterol may be increased over a long period of time are obesity and pregnancy.

Clinical and experimental evidence seems to support the view that blood lipids parallel rather closely blood fats, so it is not hard to understand the formation of gallstones in patients covered with a thick layer of fat.

Pregnancy is the other common condition in which a long continued hypercholesterolemia occurs. The increase begins as early as the second or third month and continues until after delivery (Fig. 1).

The finding of the increased cholesterol in the blood has brought forth many interesting theories as to its cause. Fluhmann¹⁰ has recently reviewed the subject in a most thorough manner. He presents the main theories as follows:

1. Those dealing with the excretion of bile. Some observers¹¹ by analysis of bile obtained by duodenal tube, have found a decrease in biliary cholesterol as pregnancy progressed. This they attributed to a damming back of cholesterol in the blood by the liver cells, and so accounted for the hypercholesterolemia.

McNee,¹² however, studied the bile directly in three patients who died in the later months of pregnancy and found markedly increased amounts of cholesterol.

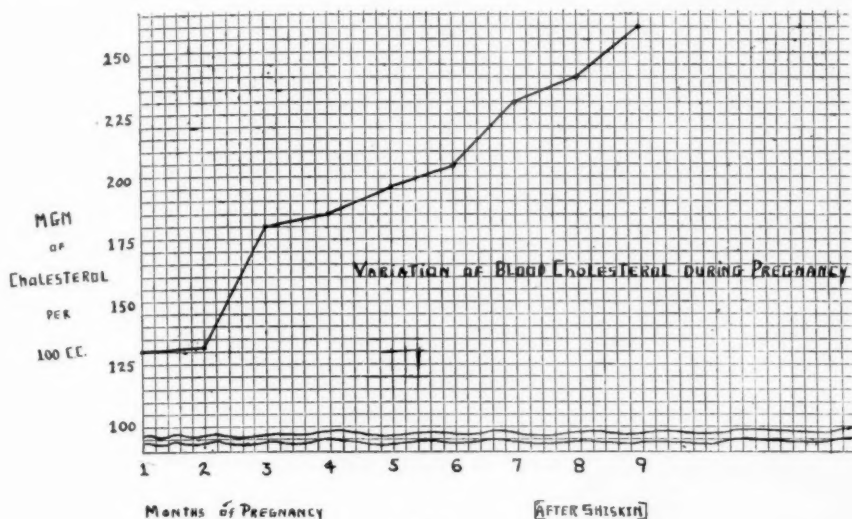


Fig. 1.

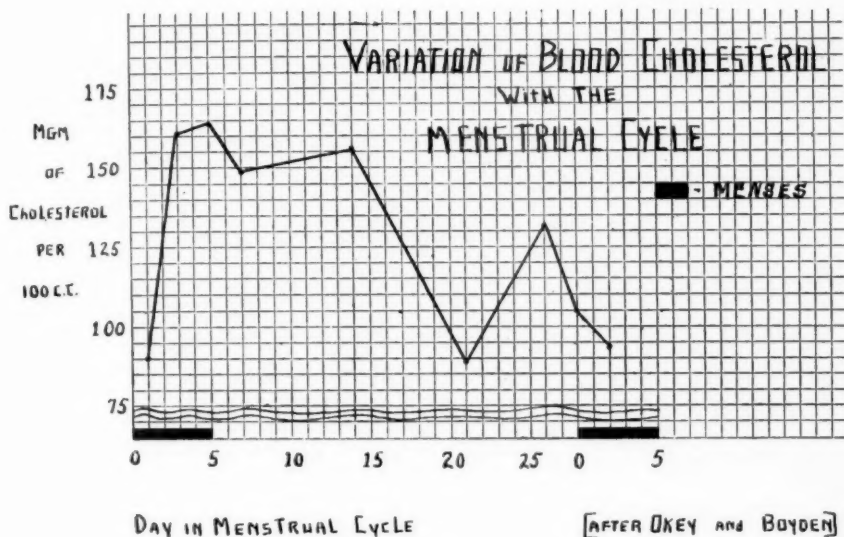


Fig. 2.

2. Those dealing with the glands of internal secretion. The ovaries are believed by Neuman and Herman¹³ to undergo a functional alteration during pregnancy "which leads to an excessive formation of cholesterol." An alteration of blood cholesterol with the onset of

menstruation has been noted by Shiskin,¹⁴ and more recently by Okey and Boyden¹⁵ (Fig. 2).

The thyroid and especially the adrenal have been looked upon as the cause of the increased blood cholesterol, because of changes in these glands associated with pregnancy.

3. Those dealing with the toxemias of pregnancy. Several cases of high blood cholesterol during eclampsia have been reported, but Slemons and Curtis¹⁶ have shown that many cases of normal pregnancy have cholesterol values still higher.

4. Those dealing with lactation. Many writers look upon the increased blood cholesterol as a preparation for lactation. (Slemons and Stander.¹⁷) They believe that the milk fats are synthesized from blood fats and lipoids, and Neuman and Herman¹³ point out that the

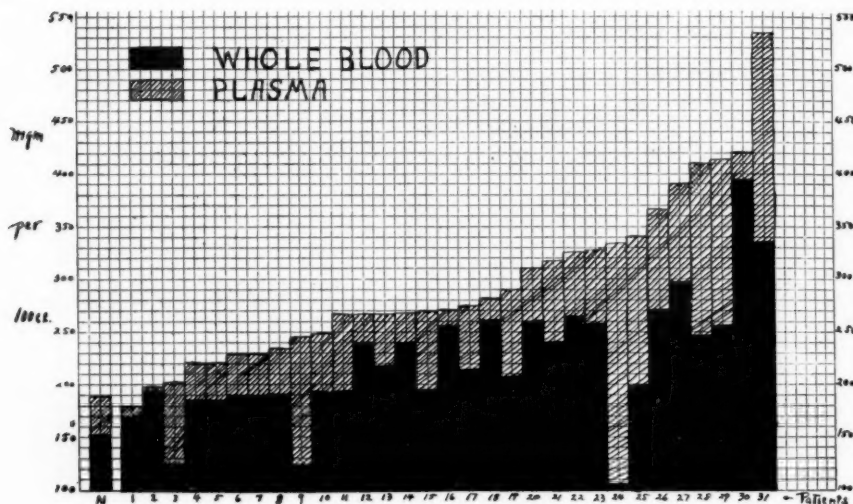


Fig. 3.—Blood cholesterol in women at term. "N" = normal values.

lipoidemia persisted for a longer time after delivery in those women who did not nurse their babies.

5. Those dealing with fetal metabolism. The question of the relationship of the fetus to the hypercholesterolemia of the mother has not been settled. It seems, however, that the fetus has little to do with this constant change in the blood of the mother.

Whatever the cause of the increase in blood cholesterol, the fact remains that the increase exists. A study of this hypercholesterolemia was made on 34 pregnant women with the idea in mind of gaining some knowledge that might be useful in the prophylactic treatment of gallstones.

Method.—Blood was collected from the patients at term; on the second, seventh and twelfth days after delivery; and at monthly intervals after delivery. In most cases the collection was made after a period of starvation, but in a few

cases, as when a patient was admitted in early labor, the collection was made without regard to starvation. The cholesterol determinations were made at once by the Oser-Karr¹⁸ modification of the Myers-Wardell method, on both the whole blood and plasma.

By this method Oser and Karr report normal cholesterol range from 140 to 170 mg. per 100 c.c. of whole blood, with an average from 21 cases of 153.7 mg. The blood plasma in their cases was found to contain an average of 68 per cent of the cholesterol in the whole blood, and their plasma values ranged from one to one and a half times as high. The average value for 21 cases was 186.8 mg. per 100 c.c. of plasma. Fig. 3 shows the cholesterol values for whole blood and plasma of 31 patients at term as compared with the average normal values.

COMMENT

Table I and Fig. 3 show the high blood cholesterol values found in nearly every case. Age or previous pregnancy seems to have no constant effect on the amount of cholesterol present.

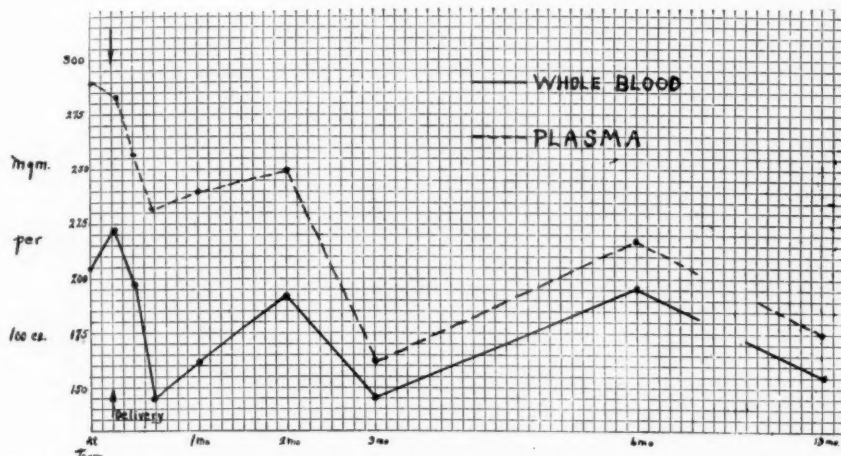


Fig. 4.—Blood cholesterol at term and after delivery. Base line represents months after delivery.

The high values found in cases of twin pregnancy may have some significance, but some of the cases of single pregnancy approached or surpassed the lower figures.

The cholesterol value does not fall immediately after delivery to the normal level, but remains high for some time. In several there was temporary increase after delivery (Fig. 4).

We have been able to follow eleven of these patients for a year and a half after delivery. Of these, eight patients (numbers 4, 6, 11, 16, 19, 20, and 27) have no symptoms. Three (numbers 8, 14, and 26) have had upper right abdominal pain and distention and belching after eating. None have had typical acute attacks of gallstone colic.

CONCLUSIONS

Since gall bladder disease occurs so frequently in females, and since the occurrence of the disease seems to bear a definite relation-

TABLE I. BLOOD CHOLESTEROL AT TERM AND AFTER DELIVERY

NO.	AGE	PARA	AT TERM	WHOLE BLOOD AFTER DELIVERY							PLASMA AFTER DELIVERY										
				2 DA.			1 MO.			2 MO.			3 MO.			6 MO.			1 YR. +		
				7 DA.	12 DA.	1 MO.	2 MO.	3 MO.	6 MO.	1 YR. +	2 DA.	7 DA.	12 DA.	1 MO.	2 MO.	3 MO.	6 MO.	1 YR. +			
3	18	0	187	220	195	212	160	170		203	163	228	240	183	234			215	163		
6	20	0	189	180	195	202						229	185	205	220						
25	19	0	240	131								265	175								
30	18	0	256									472									
7	23	1	213	150	195	170	150	193		195	150	273	170	240	165	162	250	142	175		
8	24	1	205	224	198	140	158		195	150	290	280	256	230	240			216			
13	28	1	240	207	240	240					266	334	328	320							
17	19	1	195		190	215				166	196	233	210	350					190		
26	40	1	100	259	350						233	360	390								
23	19	1	110	50	246						242	150	260								
28	26	1	245								410										
32	21	1	219								265										
1	35	2	255	215	230						327	360	240								
22	23	2	170	100	247	185					180	115	300	280					138		
14	42	2	192		190	270			200	140	268	264	220	320			131				
15	32	2	192		175	270					247		300	284	164				145		
20	21	2	185	220	235	153				162†	200	230	255	260							
24	29	2	122	171	176	207					200	230	255	260							
2	34	3	255	215	230						327	360	240								
12	29	3	396	286	268	320					420	440	346	360							
18	35	3	255	260	200						270	428	340								
27	34	3	190		340	245				175	233	360	254						206		
16	34	5	260		185	173	160			190	175	310	190	250	190			270	176		
31	39	6	264								326										
34	40	6	199								340										
21	37	8	260	205	100	120	234			178	286	230	245		290				194		
19	41	13	185	190	100					174	220	200	110						200		
Twins																					
4	30	0	335	230	203	318				223	531	308	332	328					221		
11	30	4	296	145	300	180				252*	390	240	318	210					332		
33	24	2	240								316										

*Nine months pregnant

†Three months pregnant

ship to pregnancy, it would seem that the prophylactic treatment would fall largely in the hands of the obstetrician.

Calculi, which are probably the chief cause of the symptoms and pathology in this disease, are composed largely of cholesterol in most cases. The cholesterol is obtained from that excreted in the bile and biliary cholesterol varies with the cholesterol in the blood. During pregnancy there is a definite hypercholesterolemia, which in all probability predisposes to the formation of gallstones, and may be the reason for the relationship between gall bladder disease and pregnancy. Prophylactic treatment may well be directed toward keeping the blood cholesterol at the lowest possible level at this time. The cholesterol of the blood is dependent in a large measure upon the diet, hence one method of accomplishing this purpose would be to reduce the ingestion of cholesterol-bearing foods. Such foods as fat, egg yolk, fried foods, sweetbreads, liver, kidney, pork, oily fish, butter and cheese might well be omitted from the diet, or used in extreme moderation.

The early diagnosis and surgical treatment of those cases of cholelithiasis which show symptoms during or following a pregnancy will prevent the progress of the disease, give to the surgeon a patient who is a good operative risk, and often allow the preservation of a normal gall bladder.

We wish to express our thanks to Dr. J. C. Hirst, II, of the Maternity Department of the University Hospital and to Dr. W. G. Karr, of the Laboratory of Biochemistry of the Philadelphia General Hospital, for their interest and help in the preparation of this paper.

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THE ETIOLOGIC SIGNIFICANCE OF LOWERED BLOOD-SUGAR VALUES IN VOMITING OF PREGNANCY*

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THE theory that a deficiency in carbohydrate reserves is responsible for the development of nausea and vomiting during pregnancy has a well-defined physiologic basis. This does not need to be repeated here, however, because it has become familiar from having been outlined several times previously. That it is not merely an unsubstantiated theory is demonstrated by the fact that high carbohydrate feedings and intravenous injections of glucose (dextrose) have proved so promptly and consistently beneficial in the relief of hyperemesis.

The findings recently published in a preliminary report by our group¹ which show that eclampsia is characterized by wide fluctuations in blood-sugar values and that the convulsions follow periods of what we have termed "relative hypoglycemia," have advanced definite evidence of what has long been reasonably assumed, namely, a relationship between a disturbance in carbohydrate metabolism and eclampsia.

We wish now to present evidence which we believe establishes a similar relationship between hyperemesis gravidarum and a metabolic deficiency in carbohydrates. If acceded this would likewise argue a basic etiologic relationship between the various toxic manifestations of both early and late pregnancy.

BLOOD-SUGAR STUDIES IN HYPEREMESIS

The evidence on which we base this present work is taken from a study of the initial blood-sugar values in patients entering our service with hyperemesis gravidarum (Folin-Wu technic).

For some time past the rule has been established in our clinic that a blood-sugar reading must be made on each such patient admitted before our usual active treatment may be instituted. Excepting in a few instances this specimen was taken at eight o'clock or shortly after on the morning following the patient's admission, for reasons that will be described.

In order to make conditions under which the initial blood sugar was determined in each of these cases as nearly alike as possible, namely a period of over-night fast followed by a morning reading, we have arranged certain routine procedures.

*This study is one of a series of investigations in the subject of pregnancy toxicoses being conducted under the generous provisions of the John C. Oliver Memorial Research Foundation recently established at the Laboratory of St. Margaret Memorial Hospital, Pittsburgh.

The first step in our routine general care of such patients is to establish a period of complete fast so far as the administration of food, drink, or medicine by mouth is concerned. This is continued for four to six hours, after which it is arranged to have a period of about eight hours during which the patient is given by mouth nothing more than one-half to one ounce of water every fifteen minutes even awakening her for this if necessary.

So far as possible we have arranged to have these patients admitted to the hospital in the late afternoon or early evening so that the first period could continue until midnight, the second from midnight to eight in the morning, after which the dietetic treatment of the "second twenty-four hours" could begin.

Formerly we administered glucose quite promptly by vein or by bowel, according to the seriousness of the patient's condition. Latterly, however, we have refrained from doing this until these studies could be completed, excepting of course in those few instances where the patient was in desperate condition and required immediate intravenous injection of glucose. During this preliminary fasting period the proctoclysis begun soon after admission as a routine measure is merely tap water instead of glucose as formerly.

Our chief reason, in fact, for presenting such a small series of cases as that of this present report, is that we wish to return to our previous plan of prompt administration of glucose as required and indicated rather than to have this delay which has been necessary to our studies.

Probably it would have been equally suitable to take a specimen immediately on admission because patients with hyperemesis of a degree sufficient to warrant their entering the hospital for treatment are virtually fasting when admitted. However, some of them shortly before admission might have taken and retained enough nourishment to alter their blood sugar from that of a fasting value so it was decided thus to eliminate this occasional source of error. Those patients who were so seriously ill as to require active treatment were obviously in a fasting state, and their specimens were taken at once so that the urgently needed glucose injections could be begun immediately.

It may be stated, therefore, that the blood-sugar values in this series of hyperemesis cases were determined under similar circumstances and standard conditions.

ANALYSIS OF SERIES

Forty cases were studied as has been described. In grouping them according to the severity of the condition, we have adhered to the original classification of Titus which was similar to but somewhat more rigid in its first group than that of Harding, namely, "Mild" or Group I, "Moderately severe" or Group II, and "Severe" or Group III. Among these cases under consideration there are none that even border on Group I since it is obvious that a woman who is only mildly ill with

nausea and vomiting will not be sent to the hospital for treatment. Group I patients are treated at home by dietetic instructions.

Of the forty patients thirty-two fall into Group II and eight into Group III.

TABLE I. INITIAL BLOOD-SUGAR VALUES IN HYPEREMESIS CASES (40)

BLOOD SUGAR MG. 100 C.C.	80 TO 100			TOTAL
	BELOW 80	INCL.	ABOVE 100	
Group II	18	11	3	32
Group III	7	1	0	8
All cases	25	12	3	40

It will be seen from Table I that by far the greater number show blood-sugar values below normal or average if 80 to 100 mg. is to be considered as an average nondiabetic value.

No attempt has been made to establish percentage values because of the small group of cases being presented, but the preponderance of numbers below average values is striking. In fact only one of the cases in Group III is above eighty, this patient showing 94 mg. per 100 c.c. of blood.

TABLE II. ANALYSIS OF CASES (12) SHOWING NORMAL VALUES (80 to 100 mg. sugar per 100 c.c. blood)

80-84	85-89	90-94	95-100	TOTAL
8	2	1	1	12

Even in the cases showing normal or average levels of blood sugar, the tendency as seen in Table II is toward the lower rather than the upper limits of average range.

TABLE III. ANALYSIS OF CASES (25) SHOWING VALUES BELOW 80 MG.

BLOOD SUGAR MG. 100 C.C.	20-29	30-39	40-49	50-59	60-69	70-79	TOTAL
Group II	0	0	1	1	7	10	18
Group III	1	0	1	1	1	3	7

Further elaboration of Table III should be made by stating that the six lowest readings obtained were as follows: 28 mg. (Group III); 42 mg. (Group III); 42.1 mg. (Group II); 53 mg. (Group III); 53 mg. (Group II); and 64 mg. (Group III). It is thus apparent that the lowest values were seen most often in the sickest patients.

That one patient, even though extremely ill could show such a low reading as 28 mg. without hypoglycemic convulsions might at first seem to be unlikely and to indicate some error even though the reading was carefully checked, until an opinion of Macleod² is recalled. He states in effect that the level at which hypoglycemic symptoms follow insulin administration may depend not so much on any absolute level of blood sugar as it does on the rapidity with which that level is reached.

This opinion was quoted in connection with our eclamptic blood-sugar studies to explain our term "relative hypoglycemia." We had said that eclamptic convulsions were usually preceded by sudden drops in blood sugar to levels which could be classed as relative hypoglycemia, and that these levels might hover around average or normal values as we ordinarily think of them, or even be much higher, and still be "relatively hypoglycemic" if a few moments before they had been, as we demonstrated, 50 to 80 mg. or more above that value.

The point we emphasized was that the convulsions were produced by the suddenness of this drop in blood sugar which frequently took place in no more than a few minutes' time, and that the actual level of the blood-sugar value has little or nothing to do with the phenomenon known as a hypoglycemic convulsion.

Not until after our preliminary report regarding this did we know of a paper by John³ in which he discussed hypoglycemic reactions following insulin administration occurring in a group of twenty-four diabetics. In only thirteen of these was the blood sugar at a level of 80 mg. or less, while in the remaining eleven it was above 80 mg. In five of these patients typical toxic symptoms occurred with the extraordinary blood-sugar values of 200 mg. or over. These patients undoubtedly conform to the condition which we have designated as "relative hypoglycemia" since it is obvious that their blood-sugar levels had been much higher a few moments before, and had been suddenly reduced to these other levels, still high, but relatively hypoglycemic, by the insulin which produced the reaction.

To return to the hyperemesis cases, it is equally possible for a glycogen depletion to go on in such a case even to this low level of 28 mg. without producing the familiar hypoglycemic symptoms (twitching and convulsions) because this has been such a slow process. Days and weeks have been consumed in bringing the patient to her present state, and in the meantime her nervousness and tremor are the only hypoglycemic symptoms. It is not unreasonable to think that the neurotic symptoms shown so frequently in hyperemesis may be a result of its accompanying hypoglycemia, rather than a cause of the vomiting as has been so commonly assumed.

This same degree of glycogen depletion (to a blood sugar of 28 mg.) would inevitably have caused convulsions had the process been more fulminating in its progress, as it always is in eclampsia or following insulin overdosage.

RELATIONSHIP BETWEEN VARIOUS TOXICOSES OF PREGNANCY

It is probable that herein lies one of the chief differences between the clinical manifestations of hyperemesis gravidarum and preeclampsia or eclampsia. Granting the basic underlying cause of pregnancy toxicoses to be that which we are advancing, namely, disturbance in carbohydrate metabolism on the side of a carbohydrate deficiency resulting chiefly from fetal demands, there are many influencing factors which

serve to make the clinical symptoms of toxemia of early pregnancy vary greatly from those of late pregnancy.

In early pregnancy the carbohydrate deficiency results from a combination of low carbohydrate intake on the part of the mother plus the extra burden of fetal requirements to which she was unaccustomed, this latter initiating the trouble. This opinion is constantly affirmed by inquiry into the dietetic habits and preferences of patients with hyperemesis. Almost invariably they report a preference for protein foods and an indifference or even dislike for carbohydrates, especially sweets. If this dislike does not exist the patient will usually admit having stood prolonged guard over her diet in order to reduce her weight or to remain thin.

In late pregnancy the fetal needs are even greater, and while the patient's food intake may be fairly normal for her it is likely to be poorly balanced with proteins predominating. An attack of eclampsia is usually initiated by the patient gorging on protein foods or indulging in some other dietetic indiscretion. This is therefore an acute condition, whereas the progress of hyperemesis from bad to worse is usually more gradual. Dehydration is another factor altering the picture, present in hyperemesis but absent in eclampsia.

Convulsions are the spectacular feature of toxemia of late pregnancy while vomiting is the outstanding characteristic of early pregnancy toxemia. Even though these two states are usually so different clinically an etiologic relationship is nevertheless shown by the fact that fulminating cases of hyperemesis which are called "acute yellow atrophy of the liver" will show, since here the progression is swift enough, typical "eclamptic" convulsions even though the patient may be no more than eight or ten weeks pregnant. Moreover the nephritis seen so constantly in eclampsia is imitated in severe grades of hyperemesis.

GENERAL

An attempt was made to recall these patients for blood-sugar readings six months to a year after their subsequent confinement, but only seven responded. No conclusions could be attempted, therefore.

It is interesting that the patient who showed the highest initial blood sugar of our hyperemesis series (175 mg. per 100 c.c. Group II) had a normal value of 100 mg. three months after her baby was born (she was not lactating at this time). Before her entry to the Hospital she had made an unsuccessful attempt to control her nausea and vomiting by following directions for a high carbohydrate diet at home. It is possible that this affected her initial level. She was quickly and permanently relieved in the hospital being discharged on the eighth day after admission.

For the purposes of this particular study further blood-sugar readings after an injection of glucose, or after its administration by bowel

or by mouth, are fruitless, so that in this report only these initial figures are being presented.

Half-hourly or hourly readings following an intravenous injection of glucose with the plotting of a glycemia curve as described by our group in 1922⁴ are of importance, but not in this connection so will not be discussed here.

NECESSITY FOR LABORATORY CONTROL OF TREATMENT

That careful laboratory control of these patients is essential is illustrated by the case of a patient ten weeks pregnant sent to the hospital on the natural supposition that she presented an uncomplicated case of advanced hyperemesis of pregnancy. She was emaciated and dehydrated, vomiting almost continuously, slightly jaundiced and in a muttering delirium with a heavy odor of acetone on her breath. Physical examination showed nothing more than a gingivitis, the emaciation mentioned, and the existence of an early pregnancy.

It was assumed without question that this was an ordinary case of hyperemesis gravidarum, but before giving her the first intravenous injection of glucose solution a specimen of blood was taken for blood sugar and her urine was examined.

Her blood sugar was found to be 230 mg. per 100 c.c., and the urine not only contained albumin, acetone and diacetic acid, and casts, but also gave a heavy reaction for the presence of sugar.

This was an unsuspected case of diabetic coma. But for the laboratory control the patient would have had an intravenous injection of glucose solution after which she might naturally have been classed as a severe and eventually fatal case of uncontrollable vomiting of pregnancy.

Details of treatment have been outlined elsewhere and have no place in this discussion except in respect to two points emphasized by these findings.

The lowered blood-sugar values in these cases indicate a depletion of glycogen reserves, and the reason for the benefit obtained in such cases from intravenous injections of hypertonic glucose solution is immediately apparent. As was stated in connection with our eclampsia studies the administration of insulin without glucose for any disease with a hypoglycemic basis is obviously dangerous. Moreover, to give it with the glucose is unnecessary because of the ability of this patient's pancreas to manufacture its own insulin in direct response to the sugar injection.

All of the patients reported recovered promptly under the influence of appropriate treatment, and no therapeutic abortions were necessary in this series. One patient aborted spontaneously while still in the hospital.

SUMMARY

1. The carbohydrate deficiency theory as the chief underlying factor in the causation of pregnancy toxemias has been physiologically reasonable; the success of the therapeutic measures founded on this theory has been convincing, but laboratory proof of its correctness has been lacking.

2. Recent work on the fluctuations in blood sugar during eclampsia has demonstrated that a disturbance in carbohydrate metabolism is a factor in this toxiosis of pregnancy, and that eclamptic convulsions are hypoglycemic reactions occurring at the low point of these fluctuations.

3. Blood-sugar readings taken under certain standard circumstances from patients with hyperemesis gravidarum indicate that in this condition low values predominate as a characteristic of this diseased state.

4. Even among those patients showing normal values (80 to 100 mg.) the tendency is toward the lower rather than the upper limits of the average range.

5. Such tendencies indicate a glycogen depletion in hyperemesis, previously postulated from clinical observation.

6. The lowest values indicative of the most profound glycogen depletion of the tissues are to be seen in the sickest patients.

7. Hypoglycemic levels may be attained in hyperemesis which if compared to similar values obtained more rapidly from insulin overdosage would be expected to cause convulsions, but which fail to do so because this process of glycogen depletion is a slow one. Fulminating cases of hyperemesis, or "acute yellow atrophy of the liver" frequently show convulsions early in pregnancy which are comparable to those of eclampsia, late in pregnancy.

8. The probability of an etiologic relationship between toxioses of early and of late pregnancy is strengthened by these observations and findings.

9. The reason for the successful results from the hitherto empiric treatment of hyperemesis by intravenous injections of glucose and other administration of carbohydrates is now apparent.

10. The use of insulin without glucose in hyperemesis is shown by these low sugar values to be a dangerous procedure. Its use with glucose has already been questioned.

11. Careful laboratory control of the blood chemistry of these patients with particular respect to their blood-sugar values, is essential to their treatment.

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1015 HIGHLAND BUILDING.

OBSERVATIONS ON THE BIOCHEMICAL CHANGES IN THE BLOOD FOLLOWING RADIUM THERAPY*

A REPORT OF 100 IRRADIATED CASES

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INTRODUCTION

MANY patients following exposure to radium show severe symptoms of radium sickness, manifested by nausea and vomiting. Others show very little or no discomfort. Inasmuch as a certain number of irradiated patients show a reaction which is not accounted for on a definite basis, chemical observations were made on the blood and urine of 100 patients who were treated with radium on the gynecologic service at the Long Island College Hospital with the hope of establishing some hitherto unknown relationship between the reaction and chemical changes in the blood.

The reactions following irradiation with radium or x-ray have been explained in various ways. The more important of these theories may be tabulated under the following headings: (1) intoxication; (2) acidosis; (3) metabolism; (4) inhalation; (5) enzyme; and (6) nephritic. These we may well review at this point.

1. *Intoxication*.—Edsall and Pemberton advanced the belief that roentgen rays produced a constitutional reaction, which they ascribe to an acute intoxication. Their explanation being that the roentgen rays destroyed tissue which was rich in nucleoprotein. The decomposition products of this form of protein were more or less toxic and difficult to excrete. They also added that the intoxication was independent of any alteration of excreting power of the kidneys. Linser and Sick, Engel and others, have claimed that the roentgen rays produced a roentgen toxin in the blood which might be responsible for the protein destruction.

2. *Acidosis*.—Lange believed that the reaction was a result of an acidosis which he based on cellular degeneration, an increased catabolism. Because of this belief, he employed sodium bicarbonate in large doses to overcome the constitutional effects. The work of Denis, Alrich and Martin supported this idea, for they observed an acidosis in rabbits when some portion of the intestinal canal was included within the irradiated area. Hirsh and Peterson found a disturbance of the acid-base equilibrium as manifested immediately after treatment by an increased hydrogen-ion concentration and sometimes by a slight lowering of alkali reserve. In the blood, however, these relationships were reversed twenty-four hours later. There was diminished hydrogen-ion concentration and an increased alkali reserve.

These latter results are in accordance with those obtained by Hussey in rabbits. The latter observer believed the mechanism of increased alkalinity of the blood to

*Read before the New York Obstetrical Society, December 13, 1927.

be the result of a transient acidosis produced. Golden from observations on patients treated and on dogs exposed experimentally to roentgen ray found no diminution of alkali reserve.

3. *Metabolism.*—As regards metabolism studies of persons treated with roentgen rays or radium, numerous contributions have been made on the study of leucemic patients. The work of Keymling and Murphy, Means and Aub stands out. They observed that patients suffering from leucemia showed an increase in basal metabolism and usually a negative nitrogen balance. The uric acid of the blood was usually about normal and the endogenous uric acid elimination was usually increased. Goodall believed that the roentgen-ray therapy might not have a definite effect on leucemia, but it usually caused an increased elimination of nitrogen, uric acid, and purin bases. The fall in the leucocyte count did not bear any constant relationship to the elimination of nitrogenous substance. Quadroni working with rabbits and guinea pigs found a slight increase in phosphoric acid output following radiation. Block studied the metabolism of one case radiated for chronic eczema. He found an increase in the output of uric acid, phosphoric acid, and purin bodies. Benjamin and Reuss radiated one dog and they found an increase in nitrogen elimination beginning immediately and lasting several days. They found only a transient increase in the phosphoric acid. This was confirmed by Lommel who conducted similar experiments on young dogs. Linser and Sick studied five patients who were being treated—radiated for skin diseases. They showed no radiation sickness but their output showed an increase in urinary nitrogen of two or three grams, while their uric acid output was even tripled in some cases.

Hall and Whipple found an increase in total nonprotein nitrogen and urea nitrogen in the blood of dogs exposed to roentgen rays which usually increased much above normal shortly before death. The elimination of urine nitrogen was increased on the day following treatment and remained high until death. They further observed focal areas of necrosis in the lining of the small bowel, which they believed might be responsible for the general intoxication with its vomiting and diarrhea, etc.

Hirsh and Peterson after making a chemical study of the blood of patients treated with roentgen rays concluded that there was no striking or consistent alterations in the urea nitrogen, nonprotein nitrogen, uric acid, or sugar concentration of the blood after treatment. Schmitz showed that carcinoma patients with severe reaction following roentgen-ray and radium radiation had an increase in the blood nonprotein nitrogen. He believes that "radiation sickness" is caused by the absorption of autolytic products from the degenerative areas of the tumor mass and considers the reaction to be nonspecific.

4. *Inhalation.*—Pfahler, and later Wilbert, advanced the theory that the constitutional symptoms were the result of inhalation of certain gases (ozone) produced in the air by the action of the high tension current.

5. *Enzyme.*—Heile believed that the destruction of white blood cells resulted in the release of a great store of intracellular enzymes which then attacked various tissue to produce the protein destruction noted. Baerman and Linser, Rosenstein, Edsall have suggested that roentgen rays might have stimulating action on enzyme activity in general and particularly in those cases on enzymes which produce tissue autolysis. There are observations which indicate that body ferments in the living tissues are actually influenced by the roentgen rays. Heile observed that a spleen removed from a radiated animal showed more rapid autolysis than the control. Hall and Whipple showed that the same phenomena occurred when intestinal mucous membrane was exposed to roentgen rays. Richards, in his extensive work on the effect of roentgen rays on ferments, demonstrated that a short radiation accelerated

enzyme activity, while a longer radiation inhibited it. This point is disputed by Richter and Gerhartz who maintain that roentgen rays have absolutely no effect on ferments. Wohlgenuth working with the effect of radium emanations on enzyme activity showed that radium rays stimulated the autolysis of tuberculous tissue in vitro. Newberg demonstrated that fresh carcinoma tissue autolysis more rapidly in vitro under the influence of the radium emanations than does a control not so exposed.

6. *Nephritic*.—Some workers have attempted to explain the constitutional effects following roentgen-ray radiation on the basis of a production of a nephritis. Schleip and Hildebrand, Von Jakseh, Heyman, Probram and Rotsky, Linser and Helber, Rosenstern, Warthin and others, belong to this school. Negative findings as to the production of a nephritis following radiation have been reported by Buschke and Schmidt, Krause and Ziegler, Hall and Whipple and their associates, and many others. McQuarrie and Whipple from the studies on dogs exposed to roentgen rays were forced to conclude that the kidney epithelium was much more resistant to x-ray injury than was the epithelium of small intestine; further that moderate doses of roentgen rays given repeatedly over considerable periods of time had no demonstrable influence on renal function or structure.

Routinely, all gynecologic patients enter the Long Island College Hospital at least forty-eight hours prior to operation. During this period a careful study of the patient is made. This includes a complete history and physical examination, blood pressure, urine, kidney function, examination of the blood, sedimentation time, and any other diagnostic procedures which may add to complete work-up of the case. Besides this routine on the 100 cases which contribute the data for this paper, a pre- and postoperative blood chemistry was done on all cases where radium was to be used. The blood was drawn from the median basilic vein of the arm before breakfast on the morning preceding radiation. The diet of these patients prior to radiation was the usual hospital soft diet, chiefly carbohydrates. During the treatment and postradium period, food was allowed as tolerated, starting with fluids and selected soft diet. Immediately upon the removal of the radium or within six hours after its removal, another blood specimen was taken. The urea, urea nitrogen, uric acid, creatinine and sugar of the blood thus obtained were determined according to the method of Folin and Wu. The CO_2 combining power of the blood plasma was determined according to the method of Van Slyke. A routine Wassermann examination was done in these cases. A postoperative radiation urine analysis was also included. From the time of insertion of the radium and for two or three days after its removal, these patients were carefully watched for the appearance of any unusual symptom and particularly for the so-called "radium sickness" (nausea and vomiting).

In Tables I to IX, we have attempted to give our results without any attempt at description, except the captions appearing below each table, thus eliminating unnecessary repetition and a saving of much valuable time for the reader.

TABLE I. GENERAL CLASSIFICATION OF THE CASES FOR STUDY. BENIGN 62 CASES, MALIGNANT 37 CASES, AND UNCLASSIFIED 1 CASE




BENIGN		62 CASES
MALIGNANT		37 CASES
UNCLASSIFIED		1 CASE

TABLE II. SHOWS A GROUPING OF THE CASES ACCORDING TO DIAGNOSIS, CARCINOMA OF CERVIX, FIBROID UTERUS, AND ENDOMETRIAL HYPERPLASIA COMPRISE THE LARGER GROUPS

DIAGNOSIS	NO. OF CASES
CARCINOMA OF PERINEUM	1
CARCINOMA OF CERVIX	22
RECURRENT CA OF CERVIX	5
ADENOCARCINOMA OF UTERUS	8
CARCINOMA OF RECTUM	1
URETHRAL CARUNCLE	2
CERVICAL POLYP	4
FIBROID UTERUS	16
ENDOMETRIAL HYPERPLASIA	16
HYPERPLASTIC ENDOMETRITIS	14
POLYPOID ENDOMETRITIS	7
SUBACUTE INFLAM. ENDOMETRITIS	3
SPERMATOCYTOGENOUS LEUKEMIA	1

TABLE III. AMOUNT OF RADIATION USED: 1200, 1800, 2000, AND 3000 MG. HR. DOSAGE PREDOMINATE

RADIATION	NO. OF CASES
200 MHRS.	1
250 "	2
400 "	4
500 "	4
600 "	3
750 "	1
800 "	4
1000 "	3
1200 "	20
1350 "	2
1500 "	8
1600 "	1
1800 "	10
2000 "	10
2025 "	2
2250 "	4
2400 "	5
2500 "	4
3000 "	12

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TABLE IV. NUMBER OF CASES SHOWING RADIUM SICKNESS (NAUSEA AND VOMITING)



REACTION		41 CASES
NO REACTION		59 CASES

TABLE V. RELATION BETWEEN INCREASED BLOOD UREA AND REACTION




REACTION 41 CASES		7.8 MG. PER 100 CC. OF BLOOD
NO REACTION 59 CASES		6.2 MG. PER 100 CC. OF BLOOD
AVERAGE 100 CASES		7 MG. PER 100 CC. OF BLOOD

TABLE VI. SHOWS OCCURRENCE OF ALBUMINURIA IN THE 100 CASES. BEFORE IRRADIATION THERE WERE 11 CASES THAT HAD AN ALBUMINURIA OF SOME DEGREE, WHEREAS AFTER IRRADIATION THERE WERE 12 CASES, SHOWING AN INCREASE OF ONLY 1 CASE AS A RESULT OF IRRADIATION OR ANESTHESIA OR PERHAPS BOTH

PRE-RADIATION		11 CASES
POST-RADIATION		12 CASES

TABLE VII. GENERAL CLASSIFICATION OF CASES USED WITH RELATION TO REACTION AND RISE IN BLOOD UREA

	NO. OF CASES	REACTION	INCREASE IN BLOOD UREA QUANTITY
Benign	62	30	60
Malignant	37	10	35
Unclassified	1	1	1
Total	100	41	96

TABLE VIII. TIME AND TYPE OF ANESTHESIA EMPLOYED AND THEIR RELATIONSHIP TO THE RISE IN BLOOD UREA

TYPE OF ANESTHESIA	NO. OF CASES	TIME OF OPERATION	INCREASE IN BLOOD UREA QUANTITY
Nitrous Oxide	16	27 min.	16
Nitrous Oxide and Ether	81	30 min.	78
Ether	1	22 min.	1
Chloroform	1	20 min.	1
No Anesthesia	1	---	---
Total	100		96

TABLE IX. COMPARISON OF THE AVERAGE PRERADIUM AND POSTRADIUM BLOOD UREA, UREA NITROGEN, URIC ACID, CREATININE, AND THE VARIATION. FOLLOWING TREATMENT THERE WAS AN AVERAGE INCREASE OF THE BLOOD UREA 20 PER CENT, UREA NITROGEN 20 PER CENT, URIC ACID 14 PER CENT, CREATININE 13.3 PER CENT, AND ALKALI RESERVE (CO₂) 11.6 PER CENT

	UREA	UREA N.	URIC ACID	CREATININE	ALKALI R. (CO ₂)
Before treatment	33.7	15.80	2.65	1.15	43
After treatment	40.7	19.04	3.02	1.70	48
Variation	7.0	3.22	0.37	0.20	5
Percentage increase after radium	20%	20%	14%	13.3%	11.6%

From this study we believe the following deductions may be formulated:

1. Forty-one per cent of our cases showed a mild reaction which might have been due in part to the preoperative atropine and morphine and the anesthetic.
2. Blood urea was elevated slightly in both benign and malignant conditions following radium irradiation.
3. No definite relationship could be established between the increase in the blood urea and the reaction.
4. The CO₂ combining power of the blood was not affected by irradiation.
5. The chemical and laboratory findings did not indicate any evidence of renal impairment following irradiation.

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643 ST. MARKS AVENUE.

(For discussion, see page 124.)

INTRAABDOMINAL HEMORRHAGE FROM RUPTURE OF A UTERINE VEIN DURING PREGNANCY

By JAMES RAGLAN MILLER, M.D., F.A.C.S., HARTFORD, CONN.

HEMORRHAGE into the abdominal cavity is a rare but very serious accident of pregnancy. I wish to report one such case which recovered after an operation done under a mistaken diagnosis of separation of the normally implanted placenta. Study of the literature which is presented herewith shows that the diagnosis might be made more often if only the possibility were kept in mind.

The patient was a primipara, about thirty-one weeks pregnant, thirty-one years of age, admitted to the Hartford Hospital in labor on July 1, 1927. Her physician, Dr. A. R. Couch, was called to see her at 6 A.M. because of a sudden sharp lower abdominal pain. She had previously been under his care and pregnancy had progressed normally. There had been no deviations from normal in the blood pressure, urine, or physical signs. Dr. Couch noted when he first saw her that she was having irregular contractions of the uterus and that the abdomen was unusually tender, almost rigid. Using very careful aseptic precautions he examined vaginally and found that the external os admitted one finger, the canal was partly obliterated and the membranes did not bulge. He brought her at once to the hospital, and I feel that it was due to his prompt action that we are able to report such a happy result.

I saw the patient in consultation at 11 A.M. and noted likewise that the abdomen was extremely tender and that ineffectual contractions of the uterus were present. The entire uterus appeared to be very sensitive and tense but it lacked something of the ligneous consistency which one observes in cases of intrauterine concealed hemorrhage. Her general condition was good, pulse rate was 80 and of fair quality and she showed no pallor. Another very careful examination was made which confirmed previous findings, though I noted two small dark-colored blood clots. I thereupon made a diagnosis of premature separation of the normally implanted placenta with concealed hemorrhage and ordered the patient prepared for cesarean section. Operation was started at noon, by which time the patient's blood pressure was 90/50. Intravenous saline was given during the operation.

Under gas-oxygen-ether anesthesia a lower midline incision was made. On opening the abdomen a large amount of free unclotted blood was found, estimated at 600 to 900 c.c. A premature child of about 31 weeks' development was removed by classic cesarean section. The child died a few hours later. The placenta was removed without difficulty and showed no area of separation. Careful inspection of the uterine wall showed no trace of intramural hemorrhage and the uterine incision was closed in layers with No. 2 plain and chromic catgut. After removing the fluid blood two or three organized blood clots were removed from the pelvis and separated from loose omental attachments. These clots appeared to be much older and were considered to have originated about the time of a previous attack of pain which the patient later reported had occurred five days before her present illness. Both tubes and ovaries were normal. A brisk venous hemorrhage was observed coming from a dilated vein situated about 1 cm. from the right uterine horn behind it and toward the midline. This was easily controlled with a single catgut suture. No other source of hemorrhage could be seen and the abdomen was closed.

The patient's condition was better at the close of the operation than at the beginning, pulse rate 85, systolic blood pressure 100. She had been given 1/6 gr. of

morphine and one ampoule of pituitrin and one of ernutin just before the operation. The puerperium was moderately febrile for the first four days. Wound healing was excellent, and she was discharged from the hospital twenty-two days after the operation with a final diagnosis of intraabdominal hemorrhage from a uterine vein, 31 weeks' pregnancy, puerperal endometritis following cesarean section, secondary anemia. She was advised to have a cesarean section with any subsequent labor.

The first case which I found reported in the literature was that of Fritsch¹ in 1877. This patient was twenty-eight years of age, para iii. When he first saw her, pain was confined to the abdomen and uterine contractions were present but were not very marked. Because of an increase in respiration and pulse rate he examined the heart and lungs and found nothing abnormal. There was no fever, the cervix was two fingers dilated, buttocks presenting and a good prognosis was given, the patient being left in charge of a midwife. Twelve hours later he received word that she had died. "The midwife reported that she had gone on with weak pains, became more pale, failed rapidly and died." Autopsy was performed by Marchand who found a large amount of fluid and coagulated blood in the abdomen. On the left posterior part of the true pelvis where the peritoneum began to pass over the uterus there was a small opening. The sides of the uterus were covered with very large thin walled veins. A hole in the peritoneum was seen which measured 8 mm., the edges were reddened and rough and access was had immediately into a large vein. The hole in the vein itself measured 4 mm. Examination of the edges with a lens showed that they appeared to be eroded. Fritsch was inclined to believe that this was caused by pressure necrosis by some fetal part though he admitted he came to this conclusion for want of a better explanation.

In Fritsch's case the hemorrhage came from a varicose vein which did not lie in the uterine body itself but just outside. It would appear that signs of internal hemorrhage might have been detected in time to save the patient's life had she been under the observation of some one alert to this possibility.

Leopold² in 1901 reports a case of rupture of a parametrial vessel during labor with fatal outcome. This patient had a flat rickety pelvis, was at full term and had a difficult delivery by version and extraction after a contraction ring that developed. The child died a few minutes later, the uterus contracted well, there was no external bleeding and the placenta came away intact. Careful inspection of the birth canal showed no tears as far as could be seen into the cervix. One hour later the pulse was noted as small and the patient was quite restless. There was no external bleeding. Salt solution was given and there developed a soft tumor in the region of the right broad ligament leading to the suspicion that rupture of the uterus had occurred. Internal examination disclosed no point of rupture. However, in the presence of an undoubted rupture of some blood vessel in the broad ligament, the uterus was packed and pressure exerted against the broad ligament. The patient failed rapidly, however, and died three hours after delivery. Autopsy showed death due to anemia from hemorrhage of a uterine vein in the right broad ligament which had ruptured into the abdominal cavity. There was a tear 3 cm. long in the peritoneum of the right broad ligament but the musculature of the lower uterine segment was entirely undamaged. In this case rupture must have occurred because of violent manipulations during delivery.

In 1904, J. W. Williams³ reported the case of a woman of thirty-three years delivered six hours before he saw her by an easy low forceps operation done without anesthesia. She was a primipara and there was no hemorrhage but immediately after labor she complained of an intense tearing pain about the rectum. Morphine was given and she soon passed into collapse. Diagnosis of internal hemorrhage was made and palpation showed that the lower abdomen was filled by a round and fluctuant tumor reaching to the umbilicus, which proved not to be bladder. The uterus was well contracted, surmounting this tumor and there

was marked bulging of the left vaginal fornix with a transmitted fluctuation wave. Diagnosis of hematoma of the left broad ligament was made and though the patient was almost moribund, she was prepared for immediate operation. No communication could be found between the hematoma and the uterine canal, excluding a true rupture. The source of bleeding was found to be an oozing on the inferior surface of the bladder involving no large vessels. Ligature was impossible and the cavity was packed with gauze and the vagina was also packed for counter pressure. This patient rallied and made a satisfactory recovery.

Williams stated that hardly more than 20 cases of intrapelvic hematoma following labor are reported in the literature. The first case described was that of Deneux in 1830 who pointed out that hematoma below the pelvic floor was comparatively frequent but above the pelvic floor was extremely rare. Hugenberger in 1865 reported five cases and collected ten others from the literature, and he says since that time only isolated cases were reported, the majority dying, though a few recovered spontaneously. Williams believed that his was the first case upon which an operation was done. He pointed out that the differential diagnosis of hematoma and incomplete rupture of the uterus is not important because operative interference is demanded in either condition.

Shambacher⁴ reports a case of rupture of a varicose vein in the posterior leaf of the broad ligament during pregnancy with intraabdominal hemorrhage. Symptoms began immediately after intercourse and operation was performed four hours later. This patient recovered. This, however, was a very early tubal pregnancy and not quite comparable to our present case, although he demonstrated that the tear was in a typical varicose vein, showing a thinning of the musculature of the media with occasional absence of the musculature and even of the elastic fibers.

Teller⁵ in 1910 reported the rupture of a vessel in the right broad ligament during the course of normal labor. A large hematoma was formed which spontaneously ruptured into the peritoneal cavity with fatal outcome. This patient was forty-one years old, para viii. A distinct fixed tumor appeared at the right of the uterus and a tentative diagnosis was made of an adnexa tumor. This occurred after a normal delivery without unusual loss of blood. Convalescence progressed normally until twenty-four hours after delivery when she became distended, complained of pain in the right lower quadrant, pulse became small and rapid, she began to yawn, grew pale, and was then prepared for laparotomy. A large amount of fluid and clotted blood was removed from the abdomen and there was found a tear five cm. long in the right broad ligament in a transverse direction through which protruded a large blood clot. A diagnosis of spontaneous rupture of the uterus was entertained and a total extirpation of the uterus was attempted. The pulse was scarcely perceptible at the onset of operation and she died before it could be completed. Autopsy was obtained. All the vessels of the pelvis were examined and showed no varices or aneurysms. Examination of the extirpated uterus and right adnexa showed the musculature to be intact which excluded the diagnosis of rupture of the uterus. Cause of death was given as rupture of a varix of the right broad ligament. Microscopic examination of the vessels was normal. There was no manipulation in this case at delivery and the Credé method was not used to express the placenta.

Langes⁶ in 1913 reported a woman of thirty-two years, para ii, six weeks before term. She felt a sudden sharp pain in the abdomen as if something tore. This occurred after contractions had been noted for fifteen hours. Pains continued but grew weaker and several hours later she fainted, became pulseless and was brought into the clinic by the midwife. Fetal heart tones were 150, she was two fingers dilated, membranes intact and the breech presenting. Membranes were then ruptured and two liters of amniotic fluid escaped. She became weaker and there

developed dullness in the left flank which lead to an exploratory puncture in this region, obtaining fluid blood. She was immediately prepared for laparotomy and the hemorrhage was found to come from a hole in the serosa of the uterus on the left posterior side about 1 cm. in diameter. This bleeding was controlled and a stillborn child was delivered by cesarean section followed by amputation of the uterus. She died two hours later. Autopsy showed nothing unusual and serial sections of the wall of the uterus were also normal. There were many subperitoneal vessels some of the walls of which were perhaps a little thinner than normal and the rupture occurred in a varicosity which was immediately beneath the serosa. Langes believes that such hemorrhage may occur through external violence, hemorrhagic disease, phosphorus poison, etc., but no such explanation could be found in his case.

Langes noted that there is no sudden cessation of uterine contractions as is the case with complete rupture of the uterus but rather a gradual diminution of contractions. In these cases no external bleeding is observed. The differential diagnosis should consider the simultaneous extra- and intrauterine pregnancies and rupture of some other abdominal blood vessel such as splenic artery or an aneurysm. The chief differential diagnosis he considered to be premature separation of the normally implanted placenta. He noted the following characteristics of the intra-abdominal hemorrhage: (1) sudden tearing sensation; (2) continued labor pains; (3) external tenderness of the uterus; (4) distention of the abdomen, making abdominal palpation of the fetal parts impossible; and (5) increase in anemia. He notes no relationship with nephritis, exophthalmic goiter or other disease. In conclusion he recommends exploratory paracentesis as soon as dullness appears in the flanks. Commenting on Langes' case it is interesting to note that this patient was under observation and could have been operated in ample time to save her life. I believe that the diagnosis should be made or at least entertained before marked dullness appears in the flanks and certainly before the exploratory paracentesis would give results. At such a time the chances of recovery have already been lost.

Teneoni⁷ in 1924 reviewed in great detail serious hemorrhage from ruptured vessels of various kinds in connection with pregnancy. He reported a case of a thirty-four year old woman at term, a multipara who presented bilateral inguinal hernia and large masses of varices of the external genitalia. She was under observation in the clinic for several days before labor. She had always suffered from difficulty in respiration due to deficient cardiac action and had to sit up in bed in order to breathe comfortably. She went into labor early in the morning and a few hours later was taken with a sudden attack of shortness of breath and collapse, pulse was over 90 and quite weak. No pain or other symptoms had preceded this crisis. The abdominal walls were very sensitive but uterine contractions had undergone no modification in their rhythm, or strength, and there was no bleeding from the vagina. She received supportive treatment with cardiac stimulation and rallied somewhat. At that time the cervix was not open. Toward 4 P.M. she complained again of abdominal pain and became quite agitated. The pulse became more rapid and weak and the abdomen was much more tender to palpation. The membranes then ruptured spontaneously and about three liters of clear amniotic fluid escaped with marked improvement in the patient's comfort. Fetal heart tones were normal. Three hours later she became quite pallid and unconscious. Her pulse could scarcely be counted, respirations were very shallow, and death followed shortly thereafter. A postmortem cesarean section was done but the child was dead. Autopsy showed over a liter of fluid blood in the abdomen and a break in the peritoneum on the posterior wall of the uterus, just above the uterosacral ligaments, about 1½ cm. in diameter. A probe could be passed immediately into an enlarged vein. Sections of the uterus showed nothing ab-

normal. Tenconi calls attention to coexistence of external varices in his case. In all the cases he found in the literature, women were in more or less advanced labor when hemorrhage occurred, and a few had no previous abdominal pain. He discusses also the differential diagnosis and considers exploratory paracentesis as suggested by Langes.

Chaussier⁸ in 1891 reported a fatal intraabdominal hemorrhage from the rupture of a vein of the right ovary in a woman aged thirty in the fifth month of her fourth pregnancy. External varicose veins were also noted. She was brought in from the country in a wagon by a neighbor, and complained of severe pains in the abdomen especially on the right side. Death ensued within three hours, the lesion being discovered at autopsy.

Intraperitoneal hemorrhages of this nature associated with fibroids of the uterus were reported by Benzels⁹ who collected twelve cases from the literature and added another one of his own.

There are numerous case reports in the literature of abdominal hemorrhage during pregnancy from rupture of the splenic artery, aneurysms, etc., reported by Smith,¹⁰ Simpson,¹¹ Nelten,¹² Savor,¹³ Schwing,¹⁴ Hubbard,¹⁵ LeLorier,¹⁶ Penkert,¹⁷ and Wesenberg.¹⁸

In this connection it might be well to draw attention to the observations of Bauereisen,¹⁹ Kaufman,²⁰ Halban,²¹ and Falkan²² who have shown that a marked alteration in the vein walls may occur in the lower uterine segment which predisposes to atonic postpartum hemorrhages and is thought to account for some cervical tears and occasional spontaneous rupture of the uterus. Bauereisen reports such a case of rupture. Kaufman's case showed enormous dilatation of the veins of the body of the uterus. Halban reported enormous dilatation of the veins and capillaries in the uterine wall in a patient three months pregnant. The uterus was obtained for study by a total hysterectomy. Falkan reported finding dilated capillaries and very thin walled veins in a nonpregnant woman of twenty-nine years. The microscopic picture reminded him of a cavernous angioma of the liver.

CONCLUSIONS

I have been able to report a case of intraabdominal hemorrhage caused by rupture of a vein on the wall of the uterus during the thirty-first week of pregnancy with operation and recovery. Such cases are extremely rare and always end fatally unless prompt operation is done. None of those found in the literature have survived except in a few instances where a hematoma developing in the broad ligament called attention to the hemorrhage.

The diagnosis of concealed hemorrhage is not difficult to make and probably would be made more often and more quickly if the condition were not so rare and if the physician's attention were not absorbed in watching a process which he fully expects to be physiologic. Physicians are prone to park their powers of observation when attending a confinement.

The chief difficulties in differential diagnosis are to rule out spontaneous rupture of the uterus, though the treatment for both conditions would be operative, and second, to rule out concealed hemorrhage not into the abdomen but into the uterine cavity caused by separation of the normally implanted placenta with hemorrhagic infarction of the uterine wall. Concerning this latter condition many obstetricians feel that

cesarean section is often the procedure of choice, inasmuch as the hemorrhagic infarction of the uterus may be so severe as to preclude the normal contraction and retraction of the uterine muscle necessary for control of postpartum hemorrhage.

It would seem that cases like the one reported usually give a history of (1) acute abdominal pain followed by (2) increasing sensitiveness of the abdomen, (3) signs of internal hemorrhage, and (4) decreasing but unarrested uterine contractions.

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179 ALLYN STREET.

PUERPERAL GANGRENE OF BOTH LEGS, DOUBLE AMPUTATION. RECOVERY

By R. M. TOLL, M.D., SCRANTON, PA.

PERIPHERAL gangrene as a complication of the puerperium is a very rare occurrence, but a most serious one, ending fatally in more than half the cases. The following case has several interesting features.

Mrs. G. G., age twenty-six, married eleven years, had six children all living and well; two miscarriages. No severe illnesses of any kind. All deliveries were normal. Present one on Feb. 16, 1927, was spontaneous, with no one in attendance. Husband called in a midwife who cut the cord and expressed the placenta. On the third day she got out of bed which she had always done following her other confinements. Next day she had a chill followed by fever. Admitted to the West Side Hospital Feb. 24, 1927.

Examination on admission: a ruddy, plump, well-nourished and well-developed young woman; does not look sick. T. 101°, P. 128, R. 26. Complains of pain in right loin. Abdomen somewhat distended but soft, some tenderness in each iliac fossa. Small amount of offensive lochia. Pelvic examination negative. Heart not enlarged and free from murmurs. Lungs negative. Urinalysis negative. Wassermann negative. Blood count: R.B.C. 4,000,000, W.B.C. 9840, Hb. 80.

Both legs subsequently became involved in an extensive gangrenous process, with marked septic symptoms. Following the appearance of a line of demarcation in

each leg below the knee, amputation under ether with good results and complete recovery. Subsequently she learned to walk with two artificial legs.

Gross examination of amputated right leg: specimen consists of a gangrenous leg with a deep wide line of demarcation; skin is broken in several spots; skin of the toes and foot is dry and hard; superficial fascia in the calf necrotic; tendons and deep muscles show extensive necrosis. No thrombi in the arteries or veins but both filled with a viscous bloody fluid. No microscopic examination was made. The left leg showed the same condition.

This case would appear to fall into the class of those due to arterial obstruction from endarteritic changes brought on by infection. In this instance the infection was of a mild type.

Stein's collection together with the cases of Hicks, Entwisle, and the one now reported comprise a total of sixty-six cases of puerperal peripheral gangrene. In the vast majority, fifty-six of the total, the process affected the lower extremities.

EDEMA OF CERVIX IN PREGNANCY WITH REPORT OF A CASE

BY JAMES R. MANLEY, M.D., F.A.C.S., DULUTH, MINN.

A SLIGHT edema and softening of the cervix is normal during pregnancy. It appears during the first six weeks and does not progress further, but the condition of marked edema reported herewith is possibly of sufficient rarity to merit a description.

The patient was a well developed woman, aged thirty-two, who had borne three children; the first and second labors were instrumental and very hard, the last one spontaneous. She had one miscarriage between the second and third child at three months. Her last menses started August 14, 1926. She felt fairly well until November when she said that something seemed to protrude from the vagina. She consulted a doctor in another city where she lived at that time, and he told her it was the bladder and inserted several different varieties of ring pessary. The treatment was not very successful. This condition, which was probably a cystocele, continued until about the fifteenth of March when she consulted me stating that now something else had come out of the vagina and that it stayed out all the time and did not go back when she lay down.

Vaginal examination in lithotomy position disclosed a condition which on casual inspection had the appearance of a very marked cystocele and rectocele with an unusual amount of protrusion. Close examination showed this to be a greatly hypertrophied and edematous cervix.

The cervix extended two inches outside of the vulva, was about three inches in diameter, and was four and a fourth inches long. The body of the uterus was high up in the pelvis and did not prolapse. The vaginal fornices were well marked, there was a slight cystocele and rectocele.

The mucous membrane covering the cervix was thickened and whitish in color. It was dry and there was no ulceration.

The patient was not in any great distress and so it was decided to fit her with a cup stem pessary with perineal support. This was done with the result that when she returned in three days the hypertrophy had practically disappeared, the cervix

was about normal in length but was somewhat thicker than normal, it did not protrude on straining, but retained its place high in the vagina.

The patient wore this support until May 1 when she was advised to stop its use as labor was due in about one month. The condition did not recur, she was delivered of a healthy child May 21 with no difficulty.

The literature of this condition is not very plentiful, many of the cases being reported by foreign authors.

Turenne of Montevideo reported two cases in August, 1925, with a fairly comprehensive review of the literature. One of his cases was in labor when seen, the cervix protruded 8 cm. through the vulva during a pain, while the body of the uterus was still high; this case was delivered without trouble, the hypertrophied cervix dilating easily.

The other patient was in her seventh month and because the hypertrophied cervix was infected Turenne was induced to amputate the cervix. Labor soon started and a living child was expelled. However, the woman developed a pyemia and died about three months later with a generalized infection.

Paddock reported a case in which the condition recurred in two successive pregnancies. In the last one, labor occurred during the attack, there was considerable hemorrhage but the outcome was good.

The case of Seitz is often quoted in the literature. In this instance the patient while walking suddenly felt something protruding from the vulva. A midwife incised the tumor thinking it to be the membranes. The patient bled severely and Seitz was called. A tampon stopped the bleeding and a diagnosis of edema of the cervix was made. The rectum was full of hard feces, the bowels not having moved for seven days. After free catharsis the edema disappeared in a few days. After recovery the patient went home but again allowed herself to become constipated when the condition again recurred only to quickly disappear after emptying the lower bowel. In this case the obstinate constipation seemed to be a contributing factor.

Haultain of Edinburgh reports a case in which the patient a twenty-seven-year-old para v was delivered by his students of an 8 pound baby in four hours. Before the placenta was expelled, there was found a large mass lying at the side of the vagina which was found to be the edematous anterior lip of the cervix. The tumor diminished markedly in size during the next thirty minutes and the next morning had entirely disappeared. The etiology of this condition is obscure.

Jolly considers the cause to be of the nature of an inflammatory edema caused by toxins, infection, etc., and to be analogous to angioneurotic edema. He considers that it fits in well with known cases of angioneurotic edema occurring in other regions, and it appears and disappears suddenly, is elastic, causes no pain and leaves no relic behind.

Geyl believes that it is due to interference with the venous return caused by a kink between the lower uterine segment and the cervix. This stagnation might be aggravated by constipation as in the case of Seitz where the edema disappeared on clearing out the lower bowel.

In my case it would seem that the circulatory theory was correct because as soon as the cervix was supported and lifted up favoring free venous return the condition improved, whereas if it had been due to an angioneurotic edema the mechanical support would not have helped.

FIDELITY BUILDING.

PUERPERAL TETANUS IN HAWAII

BY GUY C. MILNOR, M.D., HONOLULU

TETANUS is a very prevalent disease in the Hawaiian Islands; much too prevalent if one considers the intelligence of the people and the value of prophylactic inoculations with antitetanic serum. Nevertheless, there have been reported to the Board of Health during the past five years, 103 cases, and since in Hawaii tetanus is not a reportable disease, this means 103 deaths from this disease.

DEATHS FROM TETANUS IN THE TERRITORY OF HAWAII

YEAR	ESTIMATED POPULATION	DEATHS	RATE PER 1000
1923	298,500	24	0.08
1924	307,100	23	0.07
1925	323,645	17	0.05
1926	328,444	21	0.06
1927	333,420	18	0.05

It is very difficult to estimate how many cases of tetanus have recovered in the past five years. A survey of our own records and those of our local hospitals leads me to believe that the death rate is above 92 per cent.

Most cases have their primary focus in puncture wounds of the foot or hand. Some have been found to originate in operative wounds as in hernia incision and upper abdominal incisions.

Puerperal tetanus is less common and a case here cited seems unusual and interesting enough to be reported.

A Japanese woman, aged thirty, after missing her October period, produced an abortion on herself by inserting into the uterus a root of the poha bush, a common shrub grown in the local gardens. This happened on October 15. She began to pass clots on October 19 (4th day) and flowed up to October 29 (14th day), with no complications. On October 30 (15th day) she felt ill for the first time with chills, headache and fever, a slight backache and some peculiar stiff sensations of the jaw. On October 31 (16th day) her backache became severe and her jaw became locked. Typical tetanus spasms began and increased in severity and frequency.

She was first seen November 3 (19th day) and examination showed extreme illness, patient's jaw locked, with spasms every three to five minutes. Temperature was 104° F., axillary. She was fully conscious and was in profuse perspiration. She suffered acutely from pain in her back. Pulse was 120 and weak. There was a dark red vaginal discharge with some odor. An examination showed a retroverted, gravid uterus, with open cervix.

She was given 60,000 units of antitoxin immediately intravenously and sent to the hospital. Morphine hypodermatically, grain $\frac{1}{4}$, and chloral by mouth, grains 20, were given. She was then sent to the surgery where a dilatation and curettage were done under chloroform anesthesia. The uterus was thoroughly irrigated with a warm peroxide of hydrogen solution, 50 per cent, followed by irrigation with 25 per cent Dakin's solution. A two-way catheter was inserted within the uterus and fixed there. This was used to make a continuous drip of Dakin's solution into the uterus.

She left the operating table in fair condition at 3:00 P.M., but died at 4:00 A.M. the next day. From the time of the operation until her death she had frequent convulsions but remained conscious until the end.

Here is a case of puerperal tetanus that might have been saved had an early diagnosis been made. Further than that it brings up for discussion again the distribution in China, Japan, Hawaii, and the west coast of the United States, of the various strains of tetanus bacilli, and the inclusions of these strains in the antigens used to prepare the antitoxic sera. Unfortunately, our efforts to isolate the bacillus in this case resulted in failure.

The bacillus perhaps entered the uterus on October 15, grew and began to produce symptoms on October 29 (14th day). The fourteen-day incubation period was of doubtful value with regard to prognosis. After this date her system was so overwhelmed with infection and toxin that the most heroic means would have failed.

One other case of puerperal tetanus has been observed by me. A Hawaiian woman, aged thirty-eight, was delivered of her eighth child in her home, by a physician. A normal delivery was reported. On the sixth day after delivery she had her first sign of tetanus and died three days later. There was no focus of infection on her body such as cuts, puncture wounds, etc. Three days after the death of the mother the child died of tetanus, the infection being on the umbilicus.

401 SOUTH BERETANIA STREET.

ACUTE LYMPHATIC LEUCEMIA WITH MYELOPHTHISIC ANEMIA COMPLICATING PREGNANCY

BY WM. ALLAN, M.D., CHARLOTTE, N. C.

LEUCEMIA as a complication of pregnancy is very unusual, but according to Bower and Clark¹ not as rare as pregnancy occurring in leucemia. Kosmak² reviews the reports of three leucemic women^{3, 4, 5} who had repeated pregnancies. Between 10 and 20 cases of myeloid leucemia complicating pregnancy have been reported, but there are less than half a dozen reported instances of lymphatic^{2, 3} leucemia as a complication of pregnancy, so that the following case seems worth recording.

A white primipara, twenty years old, five months pregnant, was referred to me July 29, 1927, by Dr. R. B. Groves of Lowell. She complained of weakness, shortness of breath, failing vision, and was drowsy and very anemic. Her family and past history were unimportant. She had last menstruated February 18 to 25, 1927, and had suffered with a good deal of nausea and vomiting since the beginning of pregnancy except during the last part of the third and early part of the fourth month. She had noticed increasing paleness since the third month and before admission, examination of her blood showed red cells 464,000, hemoglobin 20 per cent, giving a color index above 2, with white blood count 16,400, polynuclears 32 per cent, small mononuclears 12 per cent, large mononuclears 51 per cent, transitionals 2 per cent, eosinophils 3 per cent. On admission there was striking pallor of skin and mucous membranes but no icteric tint; petechiae were scattered over upper arms and chest. The eye-grounds were full of fresh hemorrhages, particularly along the course of the vessels. Heart size normal with systolic murmur at the base, rate 132, regular, blood pressure 130/55. The abdomen showed uterus reaching to umbilicus; no tenderness or scars. The spleen could not be felt. The peripheral glands were not palpable. Physical examination otherwise negative. The urine showed traces of albumin and sugar, no urobilinogen, and was microscopically

negative. Examination of the blood showed hemoglobin 10 per cent, red cells 625,000, color index 0.8; white blood count 30,400, polynuclears 25 per cent, lymphocytes 73 per cent, eosinophils 2 per cent. Given 600 c.c. of blood by direct transfusion by Dr. H. P. Barret.

July 30, 1927: Icterus index 3.9. The drowsiness and listlessness have disappeared.

August 1, 1927: No vomiting and patient is hungry. Hemoglobin 15 per cent, red count 1,310,000, color index 0.7; individual red cells seem normal; no blasts, white cells 21,300, with polynuclears 36 per cent, lymphocytes 64 per cent. Given a second direct transfusion of 600 c.c.

August 10, 1927: Blood pressure 132/64. Examination of the eye-grounds showed only one small hemorrhagic spot in each fundus whereas ten days ago the right fundus was almost entirely covered with retinal hemorrhages and there were a great many hemorrhages in the left fundus. The petechial spots on the upper arms have also disappeared. Several days ago the patient complained that the gums around one tooth bled a little, but there have been no other signs of hemorrhages. For the past ten days the patient has been in the sunshine every morning and her diet has included liver and green vegetables. Sent home August 11th.

August 20: Readmitted to Presbyterian Hospital because of nausea and fainting. Given by direct transfusion 600 c.c. of blood. August 23: Given 500 c.c. of blood.

August 25: Hemoglobin 50 per cent, red cells 2,480,000; white count 23,700. August 28: Given 400 c.c. of blood by direct transfusion, and on August 31, 750 c.c.

September 2: Hemoglobin 70 per cent, red count 3,600,000; white count 27,600, polynuclears 20 per cent, lymphocytes 80 per cent.

September 7: Hemoglobin 60 per cent, red cells 3,900,000, white count 37,200, with polynuclears 9 per cent, lymphocytes 91 per cent.

September 8: Hemorrhage into the dorsum of each foot without trauma. Phthalein kidney test 45 per cent.

September 14: Hemoglobin 50 per cent, red count 2,730,000, color index 0.9; white count 44,800, with polynuclears 10 per cent, and lymphocytes 89 per cent, myelocytes 1 per cent. Blood smear shows a moderate number of both normoblasts and megaloblasts but very little variation in size, shape or staining reactions.

September 15: Reticulated red cells 0.5 per cent as compared with 0.1 per cent a week ago. Blood platelets 70,000.

September 16: Gums bleeding today. Given a seventh transfusion of 758 c.c.

September 17: Induction of labor started. Pains continued until 4:30 A.M., September 18, when she was given morphia. During the night she vomited and complained of substernal pain on inspiration. Uterine pains started again at 5 P.M., continuing for some hours. The substernal pain became more severe, the pulse rate reached 140, regular, blood pressure 128/55; some vomiting with oozing from the gums all day. Delivered by version September 19 at 6 A.M. Child stillborn. Very little bleeding during delivery but about an hour and a half later there was a brisk postpartum hemorrhage and the uterus was packed. After this hemorrhage substernal pain disappeared but the mucous membranes still showed good color. Pulse rate 156, respiration 50, suggesting air hunger. At 10 A.M., given eighth transfusion of 400 c.c. and during this procedure the pulse rate dropped to 138 and respiration to 35. Patient remained comfortable.

September 21: Patient has been rather drowsy with bleeding gums since delivery but otherwise comfortable. Leucocyte count 137,000. Three days later the white count had gone above 200,000 with 97 per cent lymphocytes, and the patient sank into coma with deep, rapid respiration and died. Autopsy not permitted.

An autopsy on the fetus showed nothing abnormal. There was no indication of leucemia in the fetal blood.⁶

Discussion.—This patient was at first thought to be suffering from the hemolytic anemia of pregnancy, as this condition is at times accompanied by a considerable increase in the leucocytes^{7, 8, 9, 10} generally, however, an increase in neutrophils. Since this hemolytic anemia of pregnancy is curable by blood transfusion this was promptly instituted. The resolution of the retinal hemorrhages, the disappearance of the petechiae, and the decline of the leucocyte count from 30,000 to 12,900 (possibly due to dilution) in the first two weeks after transfusion all looked promising. However, at the end of three weeks it became evident that the patient was making no new red blood cells herself, but was simply living on transfused blood and her leucocyte count was slowly rising with a proportionate increase in lymphocytes. An attempt was then made by four transfusions to give her enough blood to carry on to the end of the eighth month, for the sake of improving the chances of a viable fetus. The hemoglobin and red blood count were brought up to 75 per cent of normal, and declined slowly during the fifth and sixth week of observation. She could have been carried along on transfusions apparently without trouble from the anemia, but during the seventh week of observation the hemorrhagic manifestations and the steady increase in the leucocyte count seemed to demand termination of the pregnancy. Preliminary to the induction of labor she was given a seventh direct transfusion of 750 c.c. which apparently overloaded the circulatory system as shown by the substernal pain which disappeared with the postpartum hemorrhage. Unfortunately, emptying the uterus had no favorable influence on the leucemia, which progressed rapidly to a fatal termination five days after delivery.

The most interesting phase of this case was the relation of the anemia to the leucemia. On admission the symptoms and blood picture were those of a vicious anemia with a mild leucemia. After transfusions had corrected the anemia, it gradually became evident that though red blood cells were not destroyed rapidly, yet practically no new cells were being supplied by the bone marrow. The anemia, then, was aplastic, not hemolytic. In the absence of examination postmortem, it seems probable that leucemic infiltration of the bone marrow crowded out the erythroblastic tissue, producing a myelophthisic¹¹ anemia.

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MEDICAL BUILDING.

THE PLACENTAL TRANSMISSION OF INSULIN FROM FETUS TO MOTHER

BY GEORGE T. PACK, B.S., M.D., AND DONN BARBER, B.S., TUSCALOOSA,
ALABAMA

(From the Department of Pathology, University of Alabama)

IN 1911, before Banting isolated the active principle, insulin, from the pancreas, Carlson and Drennan conducted a series of experiments purporting to show that the internal pancreatic secretion was transmitted from fetus to mother. When complete pancreatectomies were performed on gravid animals, late in pregnancy, the resultant maternal

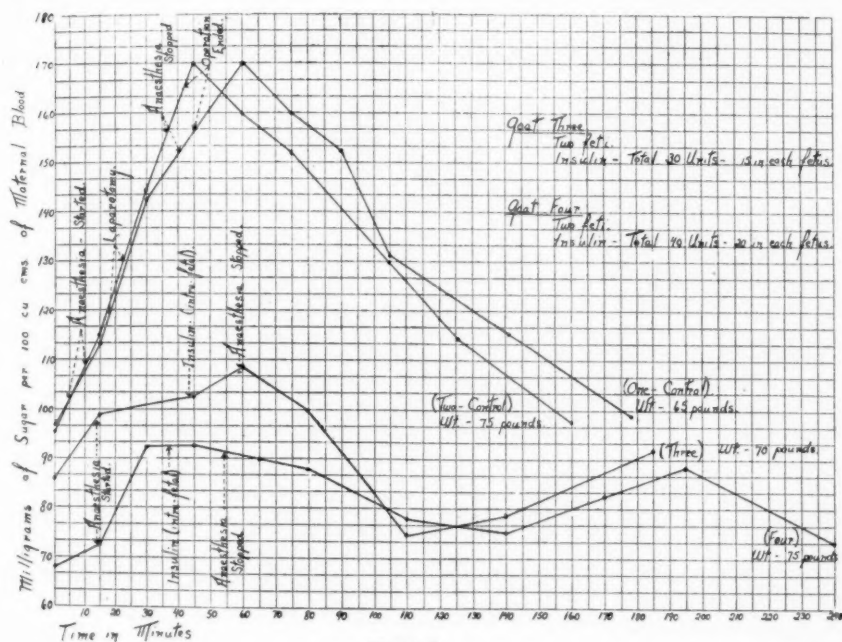


Chart I.

surgical diabetes was controlled to a significant extent by the theoretic passage of this pancreatic hormone from fetal blood through the placenta into the maternal circulation. The well-developed fetus has a pancreas rich in islet cells, and, in fact, was used as a source of insulin during the early days of insulin investigation.

The assertions made by Carlson and Drennan were logical assumptions based on indirect evidence. The research reported in this article was an attempt to obtain conclusive proof of the placental transmission of insulin by the injection of commercial insulin into the bodies of the fetu in utero and the concomitant observations of maternal blood-sugar levels.

Cats were first used, but proved unsatisfactory because of their excitability and consequent hyperglycemia. Inasmuch as the Alabamian loves his dog too dearly to part with him for research purposes, the goat was substituted because of its availability. It proved to be an acceptable experimental animal.

Method of Procedure.—Healthy pregnant goats far advanced in pregnancy were the objects of the experiment. Blood was drawn by jugular venapuncture every fifteen minutes during the course of each experiment, in order to observe any significant fluctuations in the maternal blood sugar. Blood-sugar estimations were made according to the Folin-Wu technic. After the determination of the normal blood-sugar level of each goat, ether anesthesia was induced. Previous attempts to

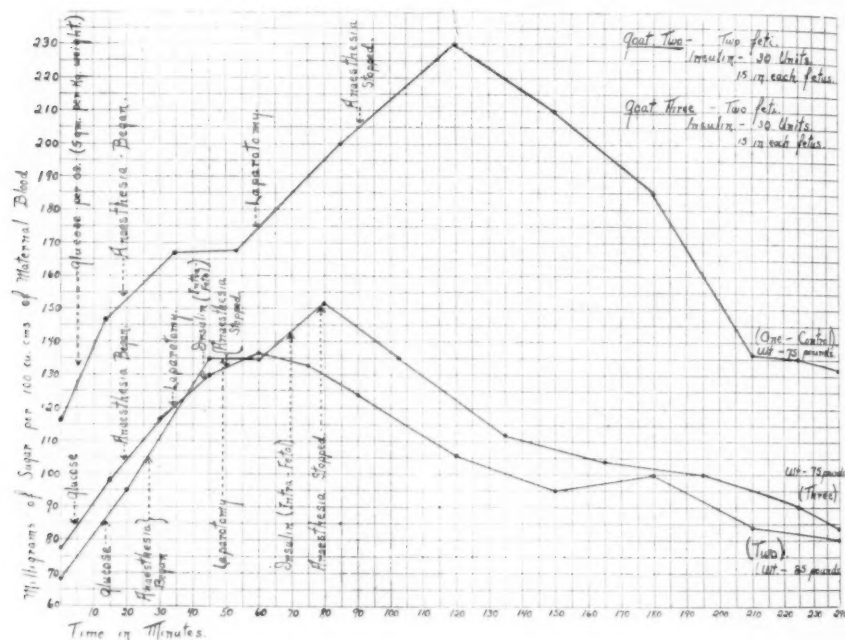


Chart II.

employ local anesthesia (novocaine) and chloroform were found to be less satisfactory than ether. With anesthesia established, a low midline laparotomy was performed, the uterus palpated and the feti counted. Then using a long finely-bored needle plugged with sterile vaseline, insulin was injected through the uterine wall into each fetus with as little trauma as possible. In no instance was hysterotomy performed. No insulin was lost in the peritoneal cavity, and the surgeon felt reasonably certain that the entire amount was introduced intrafetally. Immediate layer closure of the abdominal wound was followed by the withdrawal of ether. Aseptic precautions were used in every case and all the animals survived the operation several months, although they always went into premature labor sooner or later, and gave birth to dead feti, which had probably died from hypoglycemic shock.

Ether anesthesia elevates the blood-sugar concentration to the upper limit of normality and even beyond the renal threshold so that glycosuria may occur. (See Control-Chart I.) Insulin has far greater potency

in reducing hyperglycemia to normal than it does in converting the normal blood sugar to hypoglycemic levels. On this account, it was believed that an experimentally produced hyperglycemia of alimentary origin would furnish a more delicate indicator of insulin action. Accordingly five grams of glucose per kilogram of body weight of pregnant goats were given by stomach tube and the sugar-tolerance control obtained on several animals (See Control-Chart II.)

The results in both series of experiments were informative and significant. There is some disparity in the initial readings of the control and experimental animals, particularly in Chart II, but no more than the limits of normality permit. The ascents of the blood-sugar curves behave similarly in both series of experiments, i.e., with and without glucose, and one can readily perceive that the intrafetal injection of insulin is shortly responded to by a resultant lowering of the maternal blood sugar.

For comparative purposes we include the following protocol of a control experiment in which the goat was nonpregnant and received insulin intraperitoneally. The goat was a young animal, weighing fifty-five pounds.

TIME	MG. OF SUGAR PER 100 C.CM. OF BLOOD	REMARKS
9:25 A.M.	78.4	Normal
9:30 A.M.		Glucose—5 gm. per kg. of body weight
9:40 A.M.	98.0	
9:45 A.M.		Ether anesthesia started
9:55 A.M.	113.6	
10:10 A.M.	130.7	
10:15 A.M.		Laparotomy
10:30 A.M.	137.9	Insulin intraperitoneally. 30 Units
10:50 A.M.	133.0	Wound closure. Anesthesia ended
11:05 A.M.	113.0	
11:25 A.M.	106.0	
11:55 A.M.	96.0	
12:30 P.M.	101.0	
1:00 P.M.	85.5	
2:00 P.M.	81.3	

CONCLUSION

Insulin is transmitted through the placenta of the goat from fetus to mother, as determined by variations in maternal blood-sugar levels following intrafetal injection of commercial insulin.

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A NEW METHOD OF REMOVING A LARGE ABDOMINAL TUMOR THROUGH A SMALL INCISION IN THE ABDOMINAL WALL

By ARTHUR STEIN, M.D., F.A.C.S., NEW YORK

ONE of the disadvantages of removing large abdominal tumors is the extensive incision which we are frequently obliged to make into the abdominal wall in order to deliver the growth. In order to deliver the tumor through the smallest possible abdominal incision, I have been employing a simple maneuver which, so far as I know, has not yet been described.

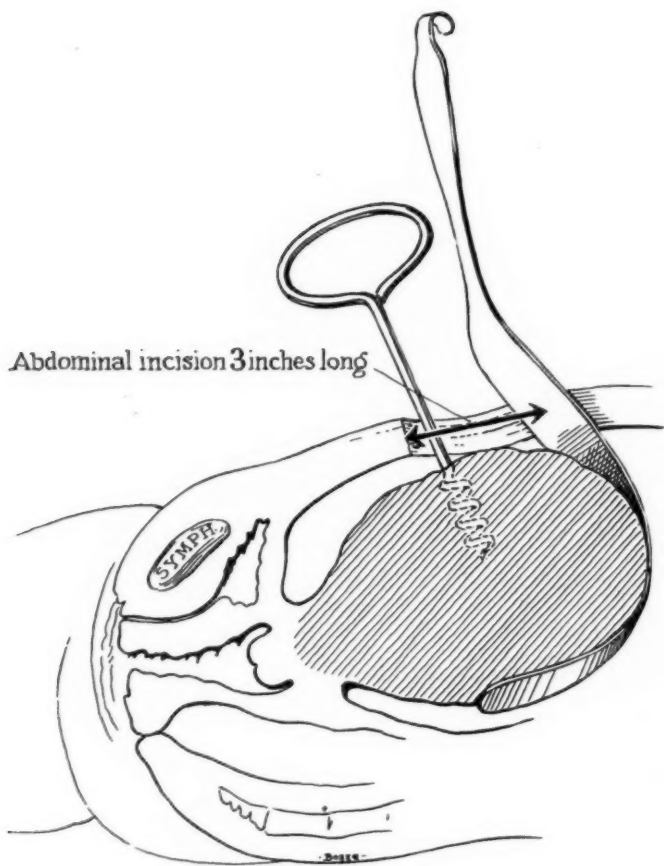


FIG. 1.

Instead of attempting to deliver the growth with the hand by passing the fingers around one of its poles, I use a No. 3 or 4 Deaver or Fritsch retractor. The blade of the retractor is passed around the growth so that the pole lies in its concavity. The difference between the thickness of the retractor and that of the hand is so considerable as to allow of a smaller incision when the instrument is used. While traction is made on the retractor, an assistant presses against both sides of the

patient's abdomen so as to facilitate delivery. Frequently this maneuver is successful in delivering the growth from the abdomen through a surprisingly small incision.

When the tumor is bound down by numerous adhesions, the method is not available, unless the adhesions can be separated first. The types of neoplasms for the removal of which it is most applicable are large uterine fibromyomas or ovarian cysts, when it is not advisable to aspirate the contents before removal.

48 EAST SEVENTY-FOURTH STREET.

A SIMPLIFIED POWDER BLOWER*

BY MAX SCHNEIDER, M.D., NEW YORK

(Assistant Adj. Gynecologist, Sydenham Hospital)

MANY cases of leucorrhea are markedly benefited by the so-called "dry treatment," which consists of thoroughly covering the vaginal mucosa with certain astringent, antiseptic, and moisture absorbing powders. These envelop the bacteria and through hygroscopic action deprive them of the moisture necessary for their existence. Thus, powders may almost have a direct curative effect upon the most frequent cause of leucorrhea, namely, bacterial infection. Furthermore, the powder treatment gives immediate subjec-

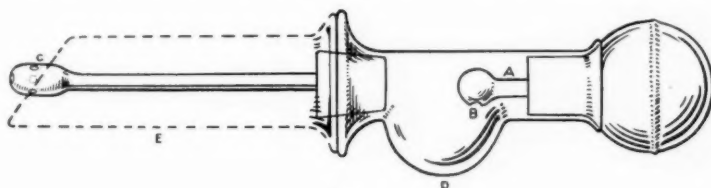


Fig. 1.

tive relief to the irritation accompanying a vaginal discharge by diminishing the amount and neutralizing the acidity.

The following is a description of a simplified powder blower, which can be easily constructed. It consists of:

1. A breast pump with small glass protector (A) in rubber bulb. In the latter there is small perforation (B) for the expulsion of the air.
2. Glass tubing, six (6) inches long, and $\frac{1}{4}$ inch in diameter.
3. A rubber stopper, $\frac{7}{8}$ inch in diameter, with one perforation large enough to hold the glass tubing.
4. A rubber bulb from a medicine dropper, in which small openings are made for the expulsion of the powder in all directions. This is placed over the outer end of the glass tubing. For this bulb, one may substitute a tubing which has a dilated end with small openings (C), as used in the vaginal douche nozzle and as illustrated in the diagram.

The rubber stopper containing the glass tubing is inserted into the large open end of the breast pump.

*This powder blower can be obtained ready-made from Becton Dickinson Co.

The small glass protector (*A*) is so placed, that the aperture (*B*) is directly above the proximal end of the powder receptacle (*D*). The latter is then filled to three-quarters of its capacity with the powder to be used and the apparatus is ready to function as a powder blower. (Gelhorn recommends equal parts of kaolin and sodium bicarbonate as a very efficient powder.)

It is advisable to use the Ferguson or tube speculum (*E*) with this method of treatment.

The advantages claimed for this instrument are evident, namely:

1. Easily constructed at a low cost.
2. It produces a powdery spray in sufficient quantities and in all directions.
3. Ease of sterilization and cleansing.

115 EAST NINETIETH STREET.

A MODIFICATION OF THE BIVALVE VAGINAL SPECULUM

BY J. BERNARD BERNSTINE, M.D., AND THAD L. MONTGOMERY, M.D.,
PHILADELPHIA, PA.

(From the Department of Obstetrics, Jefferson Medical College)

FROM our experience with the bivalve vaginal speculum, particularly in pregnancy, we believe that the anterior blade is better adapted to the contour of the cervix if it is concave at the tip instead of convex. While the posterior blade fits naturally into the concave space of the posterior fornix, the convex tipped anterior blade is opposed to the convexity of the cervix, and in the pregnant woman, to the convexity of the lower uterine segment.



As a result, the anterior blade on being opened first tends to push the cervix upward and posterior; it then scrapes by the anterior lip and imbeds itself in the anterior vaginal wall and lower uterine segment. Thereupon the cervix wedges itself farther and farther down between the two blades and becomes edematous and cyanotic.

This situation has perhaps no serious import during a brief exposure; in those cases however in which it is desired to treat disease, the necessarily more prolonged constriction and congestion of the soft pregnant cervix between the two blades, with the impingement of the anterior blade upon the lower segment may become so.

In an endeavor to obviate these undesirable features we have devised a modification of the anterior blade of the Graves type of speculum.

The modified blade is concave at its distal extremity and gently curved to adapt it to the rotundity of the cervix. Starting about one inch from the distal extremity, the superior aspect has been made concave from side to side and sloping from above downward to accommodate it to the anterior vaginal wall and lower uterine segment.

The resulting instrument has proved a true retractor of the vaginal walls, exposing the cervix without pressure or trauma and not impinging on the lower portion of the pregnant uterus. The instrument may be placed in the vagina, opened, and left in position without discomfort to the patient or danger of irritation while treatment is being proceeded with.

We have found the modified speculum no less useful in the examination and treatment of the gynecologic cervix. The principle is here no less applicable, for the convexity of the anterior wall of the cervix and uterus adjust themselves better to this concave tipped instrument.

2007 PINE STREET.
1426 SPRUCE ST.

Erratum

In the article by Breekinridge, entitled *A Frontier Nursing Service*, June, 1928, issue, in the third paragraph, page 867, the fifth sentence should read: Their median intelligence quotient was 99.6.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 6, 1927

DR. STEPHEN E. TRACY and DR. ARTHUR FIRST presented a paper entitled **A Review of One Thousand and One Obstetric Cases.** (For original article see page 51.)

DISCUSSION

DR. LONGAKER was particularly interested in the six cases of premature separation of the placenta and especially in the one which came to the hospital in a moribund condition. While he knew nothing of the individual characteristics of this particular patient, he thought the number of six cases of premature separation in 1001 cases was very large. There may be such a thing as a partial separation of a normally situated placenta. He did not think, however, that this term covered those very serious cases of premature separation of the placenta which he considered the last single case to be. Cases of abruption of the placenta form a thoroughly grave and formidable lesion. In this connection he wanted to refer to a recent case under his observation at the Kensington Hospital, very similar to the last one of this list of six cases. It should be borne in mind that the real cases of abruption of the placenta are toxic and in this case there was an actual mistake in diagnosis and a mistake which resulted in a calamity. This patient had a marked hypertension, was toxic, with systolic pressure 190. She was in very severe constant pain. She remained under the care of the house doctor under the impression that she was a case of eclampsia; instead, the patient went into syncope and continued in this condition with intense contraction of the uterus, non-intermittent, hard as a board, very tender, in which condition she was found some hours later, and pulseless. The only thing which could then be done was a section, followed by blood transfusion. The uterus had a gangrenous look when incised. The placenta was completely separated and the muscle layers dissected up and infiltrated. Nothing could save such a patient, even though the diagnosis was promptly made, short of section with hysterectomy. She rallied but died eight hours after delivery by section. She was pulseless at the time and the operation was like cutting through a cadaver. There was not enough blood left in her veins to cause any loss of blood whatever. His impression is that real cause of abruption of the placenta are infrequent and they occur in toxic cases; prompt operation is the only thing.

DR. J. O. ARNOLD wished to commend the paper from another standpoint, namely, that of reporting large series of cases in the various fields of our work in the different institutions, just as they come, and just as they are—good, bad and indifferent—so that all may draw their own conclusions, rather than the tendency to select and report only such cases as seem to support some pre-conceived notion or theory.

DR. FIRST said that one of the very interesting features is the low percentage of cesarean sections, 5 in 1001 cases. This is very unusual, especially when we

consider that at some institutions the statistics show one cesarean in every 18 or 20 cases. Ten of the cases reported had previously been delivered by cesarean section; they were delivered subsequently *per vaginam* after a labor of from twelve to twenty-four hours. They had a number of cases of definitely contracted pelvis. Several women who were told in other clinics that they would have to have cesarean section and the results reported clearly show the success of this conservatism.

DR. TRACY (closing) said that the credit for this work is due to the members of the staff. Had the collection of cases stopped at 1000 instead of at the end of the year the maternal mortality would have been just one-half that reported, as the last patient in the series did not survive a double pneumonia engrafted on a badly crippled heart.

These figures from the Post-Puerperal Clinic show what can be done for these women with proper treatment after they leave the hospital. There were 39 per cent of retrodisplacements of the uterus in the first 100 patients who reported at the clinic. With the elimination of the abdominal binder after twenty-four hours, the frequent change of positions and the knee-chest position morning and night, the incident of retrodisplacements was reduced 44 per cent.

When the patients can be made to realize the importance of following closely the instructions given, the results will be decidedly better. Many patients disregard all instructions as soon as they leave the hospital.

DRS. L. K. FERGUSON and J. T. PRIESTLEY presented a paper entitled **The Relation of Gall Bladder Disease to Pregnancy With Special Relation to the Factor of Hypercholesterolemia.** (For original article see page 82.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 13, 1927

DR. D. N. BARROWS (by invitation) presented a paper entitled **Olshausen's Operation for Retroversion, a Comparative Study of Anatomical End-Results.** (For original article see page 61.)

DISCUSSION

DR. G. G. WARD said that judging from the figures presented, the Montgomery-Simpson operation stands out very well indeed. The advantages of the Olshausen operation in the opinion of Dr. Barrows is that it is so much simpler and easier to do. That we have to grant, but, personally, he felt that the disadvantages to the Olshausen operation greatly outbalance the advantages when compared to the Montgomery-Simpson operation.

Another objection to the Olshausen operation is that it is practically similar, in the terminal results, to the old Gilliam operation in so far that it divides the abdomen into spaces, and Dr. Ward was quite sure that those who have operated over many years have all had experiences of the gut or omentum getting caught following a Gilliam operation. While this does not happen very often, still there is an anatomic condition left that is not ideal, as compared to shortening of the round ligaments in their normal direction, from the horn of the uterus to the internal ring as is done in the Montgomery-Simpson operation. For that reason he preferred

the Montgomery-Simpson operation or some similar type of operation, even though it is more difficult to do in some cases.

One of the points that Dr. Barrows brought out was in regard to a subsequent hernia. It would seem that with a silk ligature one could quite readily strangulate some of the fibers of the rectus muscle sufficiently to cause trouble.

DR. B. P. WATSON mentioned one anatomic point which has a bearing on the selection of the operation, namely, the level of the insertion of the round ligament into the uterus. If the insertion of the round ligament is low, the Olshausen operation or the Montgomery-Simpson operation will not give the result that a Baldy-Webster operation will, if the ligature is brought through and fastened well up on the back of the fundus. Dr. Watson used the Montgomery-Simpson operation very extensively and if the ligament is brought from the rectus muscle and stitched onto the under surface of the rectus sheath, there will be no pain afterwards and no trouble from the point where the ligament is fixed.

DR. BARROWS (closing) said that in six cases, in which he used chromic catgut to perform the Olshausen operation, he had four unsatisfactory results reported. Of course, the anatomic objection is the same as in the Gilliam operation. The hernia problem could be avoided by care in the insertion of the stitches.

The individual operator in each instance attempted to use the type of operation best adapted to the case, and in that way the three types were obtained from the same service. He believed that this operation is very useful in the presence of a cystocele, the principle being the same as in the Frankl operation, only on a modified scale. It may be especially valuable in cases of hysterectomy for this purpose.

DR. H. B. MATTHEWS AND DR. V. P. MAZZOLA (by invitation) presented a paper entitled **Observations on the Biochemical Changes in the Blood Following Radium Therapy, A Report of One Hundred Irradiated Cases.** (For original article see page 97.)

DISCUSSION

DR. V. P. MAZZOLA opening the discussion, said:

"A few years ago in a number of cases in which we employed radium, several had nausea and vomiting, a clinical entity, which we called radium sickness. Owing to the fact that this clinical entity was more or less inconstant, and owing to the fact that we employed various methods of treatment by alkalization and dietary measures and still we had the so-called entity of radium sickness, we endeavored to try to find out what the etiology of the so-called clinical condition was in order that we could then employ a scientific method of treatment. At that time, the thought came to us that we would check up the blood chemistry in an attempt to ascertain if in a series of cases there was any change in the nitrogenous products, so we carried out the study that Dr. Matthews has reported to us tonight. The series is a very limited one, and we cannot conclude anything definite from it, but it gives an idea of the changes that take place in the blood. At the same time it gives a clue that the reaction in itself is not the result of the said changes.

"In reviewing our data we failed to bring out the study of the blood chemistry about a week to ten days following irradiation. We thought at that time that information was not necessary because the changes in the blood chemistry immediately following irradiation were not the changes that we get following a nephritic condition, that is, a nephritic irritation, so we did not believe at that time that it was necessary to check up the blood chemistry about ten days later. However, such information would help us in a way to find out whether this increase

in urea was a persistent factor or not. The changes we found were present both in the benign and in the malignant conditions, and they were rather constant for urea.

"The slight changes we found in creatinine were so small that we attribute them to the reading of the colorimeter because two people could read a certain color and there would be variations of four or five points.

"As to the CO_2 combining power: we endeavored at the time to find out what the alkaline reserve was before and after irradiation. We found that before irradiation it was normal and following irradiation it was within normal limits, and this gave us the idea that no acidosis was present."

DR. G. G. WARD said that in his radiation work, radium sickness followed more frequently in those cases in which the radium was applied to the fundus of the uterus than if only to the cervix.

DR. G. L. MOENCH said that the symptoms which so often follow x-ray or radium applications are probably not due to changes in the urea, but the expression of some disturbance of which the urea imbalance is only a part. In working with the x-ray he found it rather easy to pick out those cases which are going to have a marked reaction. It depends (and this coincides with what Dr. Ward has said) on just how hard the intestine is hit. We can give a huge dose on the chest or on the leg with practically no intoxication, but when we x-ray the abdomen we get in most cases a very marked reaction. Naturally the severity of the reaction depends somewhat on the individual sensitiveness of the patient, but, as a general rule it is true that the stiffer the dose the greater the reaction.

Investigations have been made by Bruegel (*München. med. Wchschr.*, 1917, p. 379) which show that there are definite changes in the gastric and intestinal secretory processes following the application of x-ray or radium. He considered it would be of interest if Dr. Matthews would classify his cases, both as to dosage and point of application of the radium, that is, its relation to the intestinal tract. If, for example, we are dealing with a small uterus with the intestines close by or even adherent to the uterine body, we would expect to get a marked reaction, whereas a fairly big, lumpy fibromyoma in which the radium is applied only to the endometrium, would put a thick layer of tissue between the source of the radiant energy and the intestines and thus prevent the occurrence of marked toxic symptoms.

DR. W. P. HEALY AND DR. MAX CUTLER presented a paper entitled
Relation Between Structure and Prognosis in Cervical Carcinoma Under Radiation Treatment. (For original article see page 15.)

DISCUSSION

DR. A. PLAUT, Pathologist to the Woman's Hospital, spoke by invitation, and said that about four years ago, when Dr. Ward asked him to help the surgeons in the Woman's Hospital by grading carcinoma of the cervix on biopsy studies according to Martzloff's types he bluntly refused, stating he was not in a position to do so. Otherwise he would have graded the highly radioresistant squamous cell carcinoma as favorable and from a general biologic standpoint it seemed impossible that such a complex thing as malignant disease could be classed prognostically in such a simple way.

Going deeper into the matter he soon found himself at an impasse. For tumors which promised a fair result, according to Broder and Martzloff, on account of being highly differentiated, had to be considered resistant against radiation according to the widely accepted law of Bergonia and Tribondeau. On the other hand highly anaplastic carcinomas which were deemed very unfavorable were re-

ported melting away under radiation. Thus, a case had to be called favorable from one standpoint and unfavorable from another. The result of the investigation at the Woman's Hospital was negative as far as histologic prognosis is concerned. Neither the classification of Broder and Martzloff nor any other classification ever brought forward seemed to give a means of making a prognosis. He considered all imaginable histologic features of the carcinoma, not only the type of cell but the architecture of the whole growth, its relation to the stroma, the character of the stroma, the amount and character of inflammation, and so on. Neither any single one of these features nor any group of them seemed to be characteristic of either favorable or unfavorable cases.

After having obtained this negative result Dr. Plant went over all the slides again and classified them simply as regular, fairly regular, irregular, and very irregular. This classification was made after a rapid survey of the slide, from the general impression, not relying on any single feature. This very simple device seems to coincide with the classification used by Drs. Healy and Cutler. The same classification was used many years ago by Schottlaender and Kermauner in their classical work on carcinoma of the uterus, who decided against the feasibility of histologic prognosis.

In the Woman's Hospital, the poor results in young women were very striking. In eleven patients under thirty years of age, one lived two years and four months. All the others died before ten months elapsed. The histologic type in these cases was not uniform. Thus the constitutional factor of youth seemed more important than the histologic structure.

One histologic point cannot be omitted; many carcinomas are very anaplastic but must be called squamous cell carcinoma nevertheless. Their cells are large with distinct outlines, their arrangement corresponds fairly well to the upper layers of the skin, but the differences in size, shape, and mass relation of nucleus and plasma indicate the high degree of anaplasia. Dr. Plant was certain that such cases will react well to radiation but I did not see how one can keep them out of the squamous cell carcinoma in histologic classification.

The outstanding practical question is the following: Do Dr. Healy and Dr. Cutler recommend a biopsy and then decide whether surgery or radiation should be employed? In his opinion it follows logically from their paper that cases should be handled that way in order to do the best science can do for our cancer patients at the present time.

DR. HAROLD BAILEY said that this is a progressive step which will aid in determining what should be done in any particular case.

At the Memorial Hospital, during his service under Dr. Ewing, he became familiar with the three types of cancer the doctor has outlined. The first type used to be called acanthoma, the others plexiform epithelioma and that with marked anaplasia.

The difficulty with a study of this kind, in which we outline the prognosis, lies in the fact that it is necessary to give the full dose of radium, that is as much as the patient can really stand. For instance, in the plexiform epithelioma, although we know it is susceptible to irradiation, nevertheless, as it already extends into the lymphatics, we must give as much radium as possible in order to get as far away from the center of the cervix. Dr. Bailey called attention to another type, the embryonal type of cell, which readily succumbs to irradiation but even after three months, metastasis has already extended well out in the pelvis, and although the nearby tumor is affected by the radiation, the outskirts are still involved.

DR. G. L. MOENCH warned against too great an optimism regarding the probable results of any particular form of treatment in any particular type of tumor. It

has been attempted time and again to diagnose the degree of malignancy of a given tumor from its histologic picture, but always without success because malignancy after all is not only a morphologic but also a clinical concept, and depends very much upon the resistance which the patient's natural protective forces offer to the growth. It may be that Dr. Cutler's figures really include these differences in resistance of the individual patients inasmuch as his failures may represent not only the far advanced cases, but also those in which the resistance to the carcinoma was low. Another series of cases might result in different percentages of cures.

Some years ago Schottlaender (*Strahlentherapie*, vol. 5) reported a case of uterine carcinoma treated with radium in which a hypogastric lymph node involved by the carcinoma also showed the definite histologic changes usually accepted as typical for a radium reaction. Schottlaender interpreted these changes as being actually due to the radium and drew the conclusion that radium really acted on tissues at a greater distance than was generally believed and further that carcinoma metastases did not always offer a marked resistance to radiant energy. A short time after this Dr. Moench saw and published (*Ztschr. f. Geb. u. Gynäk.*, vol. 80) a case of plexiform uterine carcinoma which had never received any treatment of any kind and still showed the typical reaction ascribed to radiation. Schottlaender's deductions were thus more or less weakened since Dr. Moench's report showed that at times a patient, even without any treatment might in her own body develop enough resistance to affect a carcinoma in a manner similar to that of radium and that this is a point which, after all, has to be taken into consideration. We cannot and must not cling too strictly to any classification of tumors and say this type under a certain form of treatment is going to get well in this individual patient, and another type is not going to get well with the same treatment in a second patient because, after all, the patient is the primary consideration and the tumor secondary. Again, mixed types of carcinoma occur, that is tumors showing unripe, medium ripe, and ripe areas and here didactic principles of treatment must fail.

DR. I. C. RUBIN asked whether these classifications apply in the strictest sense to all the tumors examined. This will have a direct bearing in biopsies, whether we strike a portion of the tumor which happens to have a preponderance of the anaplastic, or the plexiform, or the epidermoid, or the epithelioma type.

DR. G. G. WARD called attention to the fact that when Dr. Plaut studied the cases at the Woman's Hospital on the basis of Martzloff's classification, he brought out the point Dr. Rubin just mentioned, namely, the question of how he was going to give a classification from biopsy material that would be definite, as there might be a very different condition in that part of the cervix not examined; in other words, that unless he could have the entire cervix to study it would be very difficult for him to classify the exact type of disease because it varied so in different parts of the organ.

DR. A. PLAUT referred to a typical microscopic section from the body of the uterus, which is made up of equal parts of solid carcinoma, similar to the plexiform type, of definite adenocarcinoma, and of hornified squamous cell carcinoma. This is not a very frequent occurrence, but the cases that Dr. Rubin just mentioned of adenocarcinoma of the cervix, secondarily solid, are very frequent. One might conclude from the uniform results Dr. Cutler has shown that these occurrences are not very frequent, otherwise he could not have such constant results in his tables. Dr. Plaut said he saw rather frequently adenocarcinoma which is secondarily solid, and he could not tell from the biopsy how far the tumor is composed of anaplastic parts and how far of highly differentiated parts.

DR. W. P. HEALY said it was evident that every man who has been treating carcinoma of the cervix with radiation therapy was getting results that were confusing. It was evident to him at the end of five years of observation at the Memorial Hospital that there was something in the results that we should be able to explain and that that explanation could only be given, however, by some one who was competent to study the cellular pathology of the cases and then work on the clinical side in trying to establish some deductions.

Dr. Healy considered they were fortunate in being able to compare statistics with those published by Martzloff, of Johns Hopkins, and the Mayos on the surgical treatment only, and that we must bear in mind in the future handling of cases of carcinoma of the cervix that if we are going to consider surgical treatment for even incipient carcinoma of the cervix, we must rule out the anaplastic group (because of only 9 per cent of favorable results in the early cases in that group), but you must also be prepared to meet with a high mortality as the result of operation, which is absolutely ruled out by radiation therapy in all early cases. Dr. Healy felt that there is not going to be any question about how the cases should be treated; that surgery is not going to come into play at all as the method of treatment of carcinoma of the cervix.

As to the difference in the graduation of the different groups and the difficulty of deciding sometimes in which it comes. Dr. Healy claimed there is no difficulty between Group I and Group III. The only difficulty is sometimes in deciding whether a case is plexiform, bordering on Group I, or plexiform, bordering on Group III. You may occasionally get a slide such as Dr. Plaut has alluded to, showing three different types of structure, but that is an anomaly, it is a rare occurrence, and does not enter into consideration in the final statistics.

In answer to Dr. Ward, Dr. Healy stated that they do several biopsies, sent in at different times to the laboratory, for checking up, and it is the most remarkable thing that there seldom is any question in the real outstanding cases. As far as the embryonal type is concerned, about which Dr. Bailey asked, Dr. Healy said they had discarded that term entirely; it means the anaplastic, the highly malignant third group.

DR. CUTLER (in closing) said that in regard to age, their cases failed to show any definite relation between age and prognosis, and for that reason he did not refer to it. The question that Dr. Moench raised as to the resistance of the patient is something all recognize. We know that the general condition of the patient is one of the important factors in determining the prognosis. Many of these patients come in very sick, and their general condition is poor, but the fact remains that a high proportion are cured.

In answer to Dr. Rubin, he would say that no great advances have been made in the morphologic classification of carcinoma of the cervix. In fact our classification corresponds identically with one of the very earliest classifications, namely, that of Chottlaender and Kermauner. The full significance of the relationship between these well recognized structural groups and their prognosis under radiation therapy is relatively new. As to adenocarcinoma of the cervix, they were surprised to find that of seven cases in which this diagnosis had been made, six were found to be endometrial in origin. Consequently there was only one case of true adenocarcinoma of the cervix.

We then recognized that tumors presenting this structure have invariably done badly under surgical treatment. Dr. Cutler said his interest in beginning this problem lay not so much in the clinical aspect of the subject as in its biologic phases. At the Memorial Hospital they were impressed with a group of very remarkable tumors commonly found in the tonsil, nasopharynx, and base of the tongue. Tumors in these locations present peculiar and specific histologic features,

are accompanied by a definite clinical course and display a marked susceptibility to radiation. They differ, therefore, in three important ways from squamous carcinoma, which is the common variety of intraoral lesion. Under the belief that these tumors possibly arise from transitional cells, commonly found in the crypts of the tonsil, base of the tongue and nasopharynx, the term transitional cell carcinoma was applied to them. It was later found that identically the same tumor had been described in 1921 by Schminke and by Regaud under the term lymphoepithelioma but had not been recognized in this country.

These tumors are very malignant, are highly radiosensitive and invariably recur and disseminate widely after surgical interference. The resemblance between the histologic structure of the anaplastic transitional cell carcinoma and certain carcinomas of the cervix was so impressive that it was believed that the same biologic principles could be applied. The results obtained are, therefore, not surprising but follow in logical sequence the same biologic principles which are encountered in tumors in other locations. The important question as to whether the most malignant type of carcinoma of the cervix was actually accompanied by the best prognosis under adequate radiation must be answered in the affirmative.

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 18, 1927

DR. JOSEPH L. BAER presented a specimen of **Fetus Papyraceus**.

This specimen shows how clearly the fetus can be distinguished. The atrophic placenta is well defined, measuring 8 by 10 cm., and both fetus and placenta are firmly attached to the membrane of the full-term placenta. X-ray of the fetus, the age of which is approximately fourteen weeks, shows a complete skeleton.

DR. J. B. DELEE demonstrated a means of **Rupturing the Uterus by Injection of Ether**.

He stated that in a previous meeting of the Society Dr. DeTarnowsky presented a method of producing abortion by injection of ether into the uterus. It appeared to the speaker that that was a rather dangerous procedure and after its publication he felt that something should be done to call attention to the dangers. Dr. DeLee demonstrated how the uterus might rupture following injection of ether. Into a Doremus ureometer he poured some water at a temperature of about 100°. He then injected 1 c.c. of ether, following which the maximum expansion of the ether was visible. One cubic centimeter of ether makes about 40 c.c. of gas. When a few more cubic centimeters of ether are injected it is only partially vaporized. When it is fully vaporized it will push the water out of the tube. The point he wished to make was that expansion of ether in the uterus is sufficient to rupture it if the cervix is obstructed by a blood clot or a fold of mucous membrane or if the tubes are closed. Whatever expansion of ether would take place through the patent tubes and the peritoneal cavity could not escape if the tubes were blocked.

DR. N. S. HEANEY presented a specimen of **Misplaced Endometrial Tissue**.

The patient was a married woman, twenty-nine years of age, who came in complaining of dysmenorrhea. Seven years previously she had an "appendectomy"

before which time she had never had pain at menstrual periods. After that she began to have pain in the appendix incision, which became worse as time went on. At menstrual periods the area of the scar became red and then slowly turned blue after the period was over.

On examination the uterus lay over toward the scar. The scar and the uterus could not be separated during the operation. The left ovary contained a dermoid cyst and also evidence of endometrial cysts. The uterus contained adenomata in anterior wall. Both tubes had been previously removed. The blue area in the scar was an endometrioma.

This was the ninth case Dr. Heeney had had of abdominal wound invasion with endometrial tissue.

DR. IRVING STEIN presented a new **Self-Retaining Instrument for the Patency Test and Iodized Oil Installation.**

The description of this instrument was published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. xv, May, 1928, page 707.

DR. DAVID A. HORNER reported two cases of **Inversion of the Uterus During Laparotrachelotomy.**

With an increased number of cesarean sections being performed by all sorts of operators many complications can be expected. The first case was delivered by Dr. Horner and the second by Dr. Rubovitz. Both had identical features. Both were low cervical cesarean sections. In both cases the inversion was caused by traction on the cord for removal of the placenta. Both were originally diagnosed as tumors of the uterus attached to the placental site and it was not until the invagination of the fundus was ascertained and subsequent separation of the placenta from the inverted uterus that the diagnosis was really made. They were both easily corrected by enlarging the incision through the contraction rings upward into the upper uterine segment. Both patients made uneventful recoveries, Dr. Rubovitz' patient leaving the hospital on the fifteenth day and Dr. Horner's on the twelfth despite a copious hemorrhage at the time of operation. After an extensive investigation of the literature nothing on the subject was found, therefore a new complication of obstetrics is presented to the profession. The details of these cases follow:

CASE 1 (Dr. Rubovitz). Age 31, white, married, para i. Admitted to hospital May 5, 1925, 3:30 A.M. after being in labor 2 hours. Pains strong, at 3 minute intervals. Physical examination negative except for obesity. Measurements 23-27-32-20. Blood pressure 120/80. Head floating and after 18 hours of strong pains and bag of waters ruptured showed no attempt of engage. Baby delivered by cervical cesarean section at 9:30 P.M. Ether anesthesia. In delivering placenta moderate traction resulted in inversion of the uterus through the incision in the lower uterine segment. Placenta peeled off but fundus could not be replaced until the incision was enlarged upward. The remainder of the operation was easy. Blood loss estimated 300 c.c. Progress notes show good convalescence. Highest temperature 100.6 on second day. Normal from seventh to thirteenth day. Slight reaction to 100 degrees on getting up. Discharged normal on fifteenth day.

CASE 2.—White, age 17, para i. Last menstruation end of November, 1925. At term August, 1926. Patient in good physical condition except slight edema of ankles; urine negative. Diagnosis LOA, measurements, 21, 25, 30, 18½. Sacrum shows convex curvature transversely and vertical curvature straightened and coccyx

pointing sharply forward. Diagnosis: juxtominor flat rachitic pelvis. Labor began 8 P.M., Aug. 12, 1926. Admitted to hospital 7:05 P.M., Aug. 13, 1926. Had been in labor 23 hours before admission. Baby approximately 6 pounds, and with patient in good physical condition, decided to give further test of labor. Blood pressure 118/80. On admission temperature 98.2°, pulse 96, respirations 18. Urine negative. At the end of 41 hours of unsatisfactory progress with pains of only moderate severity, but exhaustion approaching, cesarean was performed.

Operation: Ether anesthetic. The low operation (laparotrachelotomy) with delivery of the child was uneventful. Pituitrin 1 c.c., administered subcutaneously after the birth of the child. Placenta did not appear at the aperture after ten minutes of expectancy plus uterine massage. Bleeding only moderate. Traction made on cord moderately but no advance. Increased force of traction showed placenta coming through atypically. It was soon noted that the placenta was attached to a mass from which it was separated with difficulty, manually. The first suspicion was that a fibroid had been pulled through the aperture but hand applied directly to the fundus revealed the depression of an inversion. Attempt made to replace the inverted portion impossible because of tight contraction ring. Aperture enlarged by incising upward through the ring made a replacement fairly easy. Uterus packed and drained into the vagina; closed in three layers, bladder replaced, abdomen closed and patient returned to room, in good condition. Convalescence uneventful. Patient left hospital Aug. 25, 1926, with baby.

DR. J. L. BUBIS, Cleveland, Ohio, (by invitation) presented a paper entitled, **Gynoplastic Repairs of Old Lacerations Following Child-birth.** (See page 57.)

DISCUSSION

DR. J. B. DE LEE said his first attempts at secondary perineal repair were made in 1898 in women who had relaxed outlets after delivery. Then he repaired the cervix, and finally a few repairs of cystoceles. Then on the recommendation of Dr. Hirst he tried a few five days after delivery. He quickly gave this up because of the difficulty of getting proper anatomical orientation. He gave up repair of cystoceles for several reasons. In the first place it was impossible to do what he thought was a good anatomic repair. There was always excessive hemorrhage which interfered with thorough work. Unless the tissues of the broad ligament are brought together pretty nearly to the midline and above the fascia between the vagina and the midline, the repair will not be thorough. He still occasionally does a cervical repair. Secondary perineal repairs he does occasionally but not as routine. He instructs his patients to finish their reproductive careers and then come back for a thorough rehabilitation of the genitalia. He admitted that at this time repairs of the perineum do just as well, possibly better than they do in the interval, particularly third degree lacerations.

Another reason for giving up immediate repair work was that quite a number of women had infection, usually mild to be sure, but infections in the pelvis nearly always leave subsequent troubles. Again, the women do not nurse their babies as well if they have had a severe loss of blood.

DR. CAREY CULBERTSON said that it was rather common for patients who have relaxations of the pelvic floor to ask if the conditions cannot be corrected at the time the expected baby is born. As a result of that request he undertook repairs of cystoceles and perineorrhaphies, trachelorrhaphies and even amputation of the cervix, but had come practically to the same conclusion as Dr. DeLee outlined. He does not like to perform a cystocele operation immediately after labor

for the reason that the hemorrhage is profuse and there is difficulty in securing an exact anatomic orientation. Perineorrhaphy is not so difficult and the results are fairly successful. However, repair of the cervix can be done very effectively.

DR. J. P. GREENHILL asked whether Dr. Bubis used local anesthetic in some of the repairs. Repairs of cystoceles and rectoceles and trachelorrhaphy are easily done under local anesthetic.

Twice he performed a high rectocele and cystocele operation immediately after labor. In both of these the operations were more easily done than in the non-pregnant individual. The blood loss was very small. He felt that it was advisable where possible to do these operations under local anesthesia, especially because general anesthesia adds a certain, even though small, risk.

DR. N. S. HEANEY said that the more extensive the need for operative work is the less he is inclined to do it immediately after delivery since he prefers to operate upon extensive cases after involution had gone as far as possible. Occasionally, he might repair a bulging rectocele or do a trachelorrhaphy to repair a tear from a previous delivery. He is also less inclined to allow women to abort spontaneously in recent years since he prefers to inspect the cervix as a possible cause of the abortion and to carry out any necessary repair work on it while the case is still clean and while the tissues are soft and pliable. It would seem to him that it is frequently impossible to tell whether a case needed extensive repair work or not immediately after delivery. It is no infrequent experience to see a case which at the time of delivery looked as though a prolapse were going to be present, yet when this case comes to the office months after delivery the pelvis upon the closest inspection requires no operative work.

DR. J. L. BUBIS, in closing, said in reply to Dr. DeLee that he had done a great many cystocele operations and had never been troubled with excessive hemorrhage. In those cases where there was a free amount of hemorrhage he has always been able to control it. He has had better results with cystocele than with perineorrhaphy operations. These patients, of course, are hospital cases. In the hospital where one has every facility it is almost inexcusable not to examine the cervix as a routine. A bad cervix causes much more trouble than a bad perineum and even a slight nick in the cervix may be a focus of infection. It is not uncommon to find that after a patient has been subjected to numerous x-rays, the cervix has been examined and found to be the focus of infection.

When is a woman through having her last baby? If the obstetrician tells a woman she needs an operation in six months or a year, ninety-nine times out of one hundred she is not going to be operated on unless she is suffering from the effects of this condition. It is almost impossible to get a young mother into the hospital for a repair unless it is causing her trouble. By the time the infection of the cervix causes symptoms, the woman is much sicker than if she had been taken care of immediately.

DR. BUBIS used morphine and scopolamine in the early stages unless there was complete dilatation of the cervix. Some patients have as many as eight doses of scopolamine. At the time of delivery, the patient is put under deep anesthetic, generally nitrous oxide and occasionally ether. He does not use local anesthesia.

In reply to Dr. Heaney, he said that occasionally one is surprised at the condition of the mother after delivery and likewise at the change in six months. Generally, one is surprised more the other way—thinking on delivery that there is no relaxation and having the woman come back in six months or a year with more relaxation than one figured on. It has been his custom for some time to follow the same routine in abortion cases as Dr. Heaney mentioned, cauterizing the cervix or repairing it at the time the uterus is cleaned out.

DR. N. S. HEANEY spoke of his experience with the cervix as a focus of infection. The Staff at the Presbyterian Hospital, Chicago, are pioneers in the field of focal infections so that during the past years a great number of patients have been examined by him with the question in mind as to whether the cervix was the cause of a possible rheumatism, arthritis or neuritis. In not a single case has he been able to demonstrate the cervix as a focus of infection except in acute gonorrheal arthritis. A few patients requiring hysterectomy on account of menorrhagia were operated upon and since leucorrhea was present and the cervix therefore was regarded as a possible focus of infection the cervix in these cases was also removed and relief followed in not a single instance. Though by analogy the cervix might be suspected as a fruitful source of infection with systemic results, yet in his experience no single case has ever yet been proved.

DR. J. L. BUBIS, in answer to Dr. Heaney, said he had one case in mind: A woman of fifty years, always healthy, developed a severe sciatica. She had gone through the whole gamut of teeth, tonsils, sinus examinations, etc. She was three or four years past the menopause. An infected condition of the cervix was found. Within two weeks after an operation on the cervix the sciatica disappeared. Whether that was just a coincidence or not, he did not know, but he has seen similar cases clear up after operation and treatment. He could not see why the cervix was not just as liable to be a source of infection as any other focus.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D., ASSOCIATE EDITOR

Collective Review

New Books

BY ROBERT T. FRANK, A.M., M.D., F.A.C.S., NEW YORK CITY

OF GENERAL INTEREST

LEAKE, a pharmacologist and not a physician, has used *Percival's Medical Ethics*¹ as a stalking horse for his thesis which, in a somewhat more kindly spirit, resembles Bernard Shaw's introduction to the *Doctor's Dilemma*, in which that ever young Irishman says, "We make the doctor the judge, and fine him anything from sixpence to several hundred guineas if he decides in our favor."

Leake is far from being the layman which he calls himself. He is, to some degree, qualified, in my opinion, to discuss the subject at issue and shows insight, a modicum of kindness, as well as understanding throughout. He says, "The profession resists efforts to change its present relation to society." He quotes East, who calls the little guide of *Medical Ethics* issued by *The American Medical Association*, "A little guide to propriety issued by *The American Medical Association*, filled with trade-union rules . . ." What Leake really tries to show is that the rules of "Ethics" are little more than rules of etiquette developed in the profession to regulate professional contacts of the members *with each other*. He calls attention to the confusion between ethics and etiquette, which, after all, all members of the profession naturally realize fully as well as he does. However, etiquette is by no means, in my opinion, as negligible an affair as the author considers it, in guiding those whose good sense, probity, and idealism are not sufficient to do without some artificial aids. The author may at times be justified in believing that professional courtesy is confused with professional morality, and, not being in active practice, he may be unaware of how these two apparently dissimilar subjects may imply the same thing in concrete instances. By and large, "knocking" rather than minimizing the faults of colleagues is the rule with a certain type of practitioner. No one ever speaks in behalf of the calumniated physician, while much attention is focused upon the occasional glossing over of the profession's faults. Again much attention is given to the wrongdoings or mistakes, of which occasional ones see the light of day, but the physician who is sued and sometimes mulcted unjustly because of the activities of the shyster lawyer on false or trumped up malpractice charges, is rarely thought of.

According to the author, true idealism is sadly impossible in medical practice under existing conditions of human nature. This is fairly

¹*Percival's Medical Ethics*. Edited by C. D. Leake. Williams & Wilkins Co., 1927.

true, and yet, in spite of this, a surprising number of physicians, in my opinion stick to the ideal state at great personal sacrifice.

Leake traces the laws governing medical practice from Hammurapi, king of Babylon some 2200 B.C., to the present. He quotes both the pagan and Christian oath of Hippocrates.

Percival's Medical Ethics was written because of friction occurring in the Manchester Infirmary. Percival, in 1791, was asked by the trustees of the infirmary to draw up a scheme of professional conduct, which he did during the course of the next three years. This scheme is given in detail and in addition to the oath of Hippocrates, the code of ethics of *The American Medical Association* of 1847 and the principles of medical ethics of *The American Medical Association* of 1903 are included. The introductory essays by the author, delivered at the Harvard Medical School in 1927 at the suggestion of Dr. Harvey Cushing, are delightful, well worth reading, and contain much, as my discussion has attempted to show, of real value to the profession. They should be read in the proper receptive spirit and some of the suggestions, I feel sure, will blossom and bear fruit.

GYNECOLOGY

Gynecology, by Howard A. Kelly and Collaborators (22 in number), is a landmark in American gynecology.² It is a pleasure and a privilege to review this book which, in its way, may be considered the third edition of Kelly's original work on *Operative Gynecology* which appeared in 1901. The second edition in two volume form appeared in 1918. This third one volume edition, although for the first time written with the aid of collaborators, from its charming introduction to the last page, shows the unmistakable hallmark of Howard A. Kelly. Although possibly a trifle uneven in spots, a high standard of excellence prevails throughout. The book mirrors the best that can be found in American gynecology, presented in a readable, convincing form. The group of collaborators gathered by Dr. Kelly, as is readily understood, embrace mainly his immediate associates and such colleagues as came in contact with him at Johns Hopkins, but is by no means limited to these as will be shown if I mention Reuben Peterson, George Gray Ward, Lilian K. P. Farrar, Isidore Rubin, George Gellhorn, and others.

The ever young dean of American gynecology has personally contributed 17 of the 49 chapters so that the book may still be considered predominately his as heretofore. All of these chapters have been brought fully up to date, with perhaps the sole exception of that dealing with leucorrhea, in which the light shed upon the subject by modern researches, dealing with the flora of the vagina, deserves some mention.

The two chapters contributed by Ward on cystocele, prolapse, rectocele, and injury to the pelvic floor, are worth careful study. Anteriorly he favors a somewhat hybrid operation, a technic to which he attaches the syndicated names of Hadra, Goffe, Frank, Alexandroff and Sims. Somewhat to my surprise, I see that posteriorly he still utilizes a technic in which the levatores ani are actually exposed and united. This technic has been abandoned by many operators because

²*Gynecology*. By Howard A. Kelly and Collaborators. D. Appleton & Co., New York, 1928.

of the hard, painful perineal shelves resulting from it. The operation for enterocele is very well described.

The Wertheim operation for carcinoma of the cervix is beautifully illustrated, although in the text, as is the trend of modern gynecologists, radio-therapeutic treatment of the cervical canal is, on the whole, preferred.

In tumors of the ovary, dealt with by George H. Gardner and Herbert F. Trout, classification of cystic tumors according to the pathology is confusing. In serous cystadenoma, called by them simply cystadenoma, no mention of their most characteristic feature, namely the ciliation of the gland epithelium, is mentioned. The statement that pseudomucin cysts do not reach the growth proportions of the ponderous serous cysts, is contrary to all the generally accepted clinical data. The attempt to establish a distinct classification on the presence or absence of papillations appears distinctly fallacious as papillary outgrowths are, after all, ascribable to mechanical conditions rather than to any inherent properties of the epithelium. Papillations can be found in the simple follicular retention cysts, in pseudomucin cyst adenomata, as well as in the commonly occurring variety, the serous cystadenomata. Every pathologist will be willing to concede that papillations influence the clinical picture and the prognosis extremely, but I believe that most of them will agree with me that a classification based on the presence or absence of papillary outgrowths is not warranted.

Such chapters as Peruterine Tubal Insufflation by Rubin, Endometriomas by Lewis, Ureteral Stricture by Hunner, Tumors of the Bladder by Burnam and Neill, Protein Therapy by Gellhorn, Radium by Burnam, X-ray by Fricke, Pneumoperitoneal Roentgenography by Peterson, Ultraviolet Radiation by Fricke, Electrothermy by Grant E. Ward, Topics on Psychopathology by Esther Loring Richards, show the tremendous ground covered in this textbook, as well as the wide appeal that it is bound to have throughout the profession.

Few men can hope to look upon as long, active and fruitful a career as Howard A. Kelly. We hope that he will continue to exercise a guiding influence on American, and in fact, on world gynecology for many years to come. This book sums up an entire era of gynecology and is a lasting landmark in medical literature.

Schröder's monograph on the genital cycle of the human female and its disturbances³ is a most impressive contribution, complete, containing carefully selected material, much personal research which has extended over years, and a detailed search of the literature. The large clinical material which is embodied has been worked over and sifted in a most meticulous fashion. If anything, from the American point of view, the monograph is a trifle too long to be readily read. On the other hand, it is a wonderful mine of information and can be referred to for material and literature alike.

The many microphotographs, particularly of the ovary and endometrium, in a multitude of functional stages, cannot be duplicated in any other book. Fifty pages are devoted to the cycle of the lower animals. Schröder, as is well known, has elaborated and fortified the theory of menstrual endometrial desquamation by his many continued and personal researches. He submits the physiology of the female

³*Handbuch der Gynäkologie*. Herausgegeben von Dr. W. Stöckel. Erster Band. Zweite Hälfte. Der mensuelle Genitalzyklus des Weibes und seine Störungen, von Dr. R. Schröder. J. F. Bergmann, München, 1928.

sex hormone to a detailed analysis. In addition to the introductory, anatomic and physiologic portion, much careful attention has been devoted to the clinical changes which occur during both the normal cycle and in disease. He emphasizes, as he always has, the abnormal persistence of the ripening follicle and the irregular hemorrhages resulting therefrom, due to a stationary hyperplasia which he calls metropathia hemorrhagica. Endometritis, endometriosis, as well as general disturbances accompanying menstruation, are discussed. The book is a monument of accuracy based on personal research, both laboratory and clinical, and can be used as a valuable mine of information.

In the same series, Engelmann has described sterility and sterilization⁴ in the course of 279 pages. The subject is treated from every aspect most thoroughly and detailedly. Particular attention is paid to insufflation, salpingography, the various indications for stimulating doses of x-ray, after the functional and organic causes of sterility have been dealt with. The concluding portion of this monograph deals with the causes justifying sterilization and the methods employed.

The second portion of this installment, which in all represents the third volume, is the importance of constitution in gynecology by A. Mayer, a most complete monograph of 575 pages. First he takes up the difference between man and woman, then the special female characters. The changes due to marriage and pregnancy are discussed; the comparative duration of life in women and men and their psychic differences. Under pathology of constitution, the somatic types are first described, then the marked deviations, such as infantilism, in which he takes up face, hands, teeth, breasts, vulva, hair, general build, and the internal genitals themselves are dealt with. Among other conditions are asthenia, obesity, gigantism, and nanism. Tonus anomalies, intersexual and hypersexual types are next discussed. The influence of constitution on menstruation is an important and interesting phase; the early or late appearance of the menses, dysmenorrhea, sterility, disturbances of pregnancy, all come under this main heading. Next the sex of offsprings, twinning, and other fetal anomalies are mentioned. Intercurrent conditions as fluor, tuberculosis, carcinoma, the resistance to operation are discussed from the point of view of constitution. This, like Schröder's contribution, must be considered a most valuable addition to the world's literature. The sole criticism that I have to make is, that both of these monographs err on the side of too great a completeness, verging on prolixity, which does not distract from their value as reference handbooks, but will keep the average reader from perusing them from cover to cover.

The fourth edition of Faure's well-known treatise of gynecology,⁵ a large two volume affair, has just appeared. Faure today is the dean of French gynecologists and holds one of the few chairs in France strictly reserved for this specialty. The anatomic descriptions, as heretofore, are very good, including the illustrations. The chapters dealing with physiology are by no means modern or up to date. This applies especially to the description of the details of menstruation. As a direct result of this somewhat archaic physiology, the treatment of

⁴Handbuch der Gynaekologie. J. Veit-W. Stoeckel. Dritter Band. Sterilität und Sterilisation. Bedeutung der Konstitution für die Frauenheilkunde. Bearbeitet von F. Engelmann und A. Mayer. J. F. Bergmann, München, 1927.

⁵Traité de Gynecologie Medico-Chirurgicale. Quatrième édition, par J. L. Faure et A. Siredey. Gaston Doin et Cie, Paris, 1928.

functional diseases is likewise not modern. After all, to speak of "asthenopie d'origine utérine" based on a reference to Morse of 1887 (*New York Medical Journal*, 1887) is hardly excusable. Instead of references to Deuteronomy and Leviticus in regard to leucorrhea, the average reader would prefer some description of the degrees of contamination (Reinheitsgrade). The description of operations for prolapse are not complete from our point of view.

The authors feature lipiodol for the determination of tubal patency. The descriptions of medical treatment are detailed. Most conservative technics of operations are gone into quite fully and are illustrated in a striking fashion. The French literature is considered in great detail so that this volume should be an excellent source to find references to the French literature. On the whole the treatise must be considered a very well balanced gynecologic textbook. Operative indications are not stressed to the exclusion of conservative measures.

Radium in Gynecology by the late John G. Clark together with Charles C. Norris and Dr. G. Failla⁶ covers the entire subject in a manner designed to meet the requirements of the medical man and especially of the gynecologist in order to help him select the proper cases for treatment.

Although the article by Failla on physics is 100 pages in length, very interesting and clearly written, it will hardly be sufficiently detailed to act as a guide to the trained roentgenologist, but is an extremely lucid description.

The historic introduction to the subject is pleasant and informative, and shows why radium has gone down to \$70.00 a mg. with ultimate prospect of eventually reaching one-half of this price, as well as the destruction of the American radium producing companies. However, radium will always remain expensive as it is present only in 1 to 2,800,000 parts of uranium.

When used for castration by application in the uterus, 1200 mg. hours are required to act on the ovaries. This amount of application, and this I consider a serious defect of radium versus x-ray castration, will always produce a persistent leucorrhea. The authors favor biopsy for diagnosis and, in spite of theoretic danger of exploratory curettage, likewise advocate this diagnostic measure in cases suspected of corpus carcinoma.

The authors present no statistics of their own on carcinoma of the vulva and vagina. In carcinoma of the cervix, although immature types respond more readily by preliminary healing to radium, the local response being 76 per cent in comparison to 51 per cent in more mature types, the end-results in both groups are the same. Clark found that in Group 1, in which carcinoma of the cervix is limited to the uterus, radium alone cured 28.5 per cent, while radium combined with high trachelectomy by means of the cautery knife, cured 83 per cent. I notice with approval that the authors advocate preliminary curettage in all supposedly benign hemorrhages from the uterus before using radium. The sole criticism I have to make of the book is its extremely impersonal method of presentation. I would have preferred to have heard more of the personal experiences of both of the authors because of their extensive study of the subject.

Three more installments of Halban and Seitz's *Biology and Path-*

⁶*Radium in Gynecology*. By John G. Clark and Charles C. Norris. J. B. Lippincott Co., Philadelphia, 1928.

ology of Women⁷ have appeared. Installments 40 and 42 deal with Forensic Gynecology by Reuter of Graz. The German and Austrian laws are the ones considered. Consequently the American gynecologists will not derive full benefit from these monographs. However, the subject matter dealt with is, after all, applicable to the laws of any nation, with some changes. Every aspect of legal medicine in reference to gynecology is discussed in detail. Such subjects as the legal responsibility of physicians, the physician as an expert witness, are of general interest. Of special importance to gynecologists is the diagnosis of virginity and of rape, the legal indications for sterilization, the determination of stillbirth or murder of the newborn, the diagnosis of antecedent abortion, and other like subjects.

Installment 41 contains the subject of the relation of the nervous system to the genitals by J. Novak of Vienna. A good anatomic description, well illustrated, is introductory. Diseases due to menstruation and pregnancy are discussed. The author finds no increase in peripheral irritability in eclampsia. Encephalitis and pregnancy, chorea and pregnancy form interesting reading. The trauma of labor on the peripheral nerves is important. Finally, the injury to the fetal brain is carefully gone into, with illustrations. The second portion of this installment deals with the physiology and pathology of puberty in the female by Neurath of Vienna. Of interest are especially the tumors of the pineal and adrenal glands, producing premature puberty.

Cotte, successor to Polloson of Lyons,⁸ after remarking that operative technic is stabilized and standardized but that therapeutic problems continue to require elucidation, has produced this huge and massive compilation covering every aspect of the functional disturbances of the female genital tract, including physiology, clinical manifestations, and therapeutics. The treatment, while impartial and thorough throughout, lacks originality and the personal touch. An immense amount of literature is incorporated, especially from French sources, but because of the lack of an authors' index, is not readily accessible to the research student. All the newer acquirements, such as the contamination degree of fluor, insufflation, lipiodol injections, and operations for sterility, are discussed in full.

Crossen's *Gynecology for Nurses*⁹ is a concise, beautifully gotten up textbook of less than 300 pages. It is profusely illustrated from many sources. The text is nice and simple, and yet detailed. In succession the anatomy and physiology of the genital tract, gynecologic diseases, examination, treatment, both nonoperative and operative, and preparation of supplies are gone into. The entire book is very adequate, readable, and good.

Menopause and its disturbances is dealt with by Zacherl.¹⁰ He discusses the physiology and pathology of the onset of the climacterium, and attempts to point the way to recognize menopause symptoms and to weed out other similar symptoms arising from more serious pathologic disturbances, such as myoma and carcinoma. Only too often serious pathologic conditions mask themselves as climacteric disturbances, to the danger and detriment of the patient. This monograph is timely.

⁷Biologie und Pathologie des Weibes. J. Halban und L. Seltz Lieferungen 40, 41, 42. Urban & Schwarzenberg, Berlin, 1927.

⁸Troubles Fonctionnels de L'Appareil Genital de la Femme. Par G. Cotte. Masson et Cie, Paris, 1928.

⁹Gynecology for Nurses. By H. S. Crossen. C. V. Mosby Co., St. Louis, 1927.

¹⁰Die Wechseljahre der Frau. Von H. Zacherl. Julius Springer, Wien, 1928.

Tottenham's *Aids to Gynaecology*¹¹ has reached its seventh edition. This book evidently fulfills a want as its republication indicates.

OBSTETRICS

Séjourné's monograph on *Mitral Stenosis and Pregnancy*¹² emphasizes the fact that radiologic examination is necessary in order to determine the size of the left auricle which must be watched. If there is dilatation, interruption of pregnancy is indicated. He warns against using ether in emptying the uterus. Pregnancy should be forbidden in every case of mitral stenosis in which there has been an attack of edema of the lungs. About one-half of the cases are stationary and these cases may be allowed to go to term. The monograph is lavishly illustrated with roentgenograms.

Grosser, whose work on placentation has been classic for many years, has written, as part of the *Deutsche Frauenheilkunde* a general work on the development of the fetus, membranes and placenta of the human species and mammals.¹³ Considerable space is devoted to the comparative study of placentation in different species, including the very useful description of laboratory animals. The main subdivisions of the book are on progenesis, dealing with the ovum, the sperma, and fecundation; blastogenesis which deals with the early divisions of the ovum; and placentation. Seventy-five pages are devoted to the comparative aspects of this important question, the rest to the human being. The book is well illustrated, complete, and contains good references to the literature. It is a most authoritative exposition of the subject, and of particular use to medical men as a source of reference.

Vignes and Jean, with the collaboration of Robin, have issued *L'Année Obstétricale* covering 1925.¹⁴ It is a pity that so much time intervenes between the assembly and appearance of this valuable summary and digest of obstetric activities. The French editors should keep in mind and emulate the promptitude of our American year books which are in the hands of their readers only a few months after the year is completed.

The authors have shown their well-known care, reliability, and exactitude. Normal pregnancy, especially the features of diagnosis and the changes in the individual organs, are taken up. Under pathologic pregnancy, ectopic, hemorrhage during pregnancy, pernicious anemia, the toxemias and intercurrent diseases are dealt with. Abortion, tumors, labor, therapeutics are among the subjects covered. The allied subject of puericulture, the pathology of the newborn, legal obstetrics, are included. Under the heading of researches, the function of the placenta and of the pancreas during pregnancy, the Wassermann reaction as affected by pregnancy, and in pregnancy, epidemic abortion, carcinoma in pregnancy, are a few of the subjects discussed. References to the literature throughout are abundant, international and accurate.

¹¹*Aid to Gynaecology*. By R. E. Tottenham. Ed. 7. Wm. Wood & Co., New York, 1928.

¹²*Le Retrecissement Mitral dans ses Rapports avec L'Etat Puerperal*. Par J. Séjourné. Gaston Doin & Cie, Paris, 1928.

¹³*Fruchtentwicklung Eihautbildung und Placentation des Menschen und der Säugetiere*. Von Otto Grosser. *Deutsche Frauenheilkunde*. Fünfter Band. J. F. Bergmann, München, 1927.

¹⁴*L'Année Obstétricale. Travaux de 1925 et Questions Obstétricales d'Actualité*. H. Vignes et B. Jean avec la collaboration de V. Robin. Masson et Cie, 1927.

That most prolific author, L. Fraenkel, has now written a short treatise on *Social Obstetrics and Gynecology*¹⁵ designed for the guidance of physicians employed by the government in schools, institutions, hospitals, industrial lodges, legal, police, athletics, children, women, and other specialties. The scope of this small monograph is huge. It begins with the neonatus, blenorrhea of the eyes, takes up vulvovaginitis of children, life during puberty, bad habits formed in youth, such as the overloading of the bladder and the rectum. He deals with modern woman's clothes, the lightness of which he considers admirable, weighing 1 pound against 6 pounds for men. He takes up such diverse subjects as sports, injuries, including the determination of virginity, sex, pregnancy, and rape. Marriage and its duties are discussed. Work, fertility, and sterility, the guidance during pregnancy, instruction in gynecology and obstetrics, etc., are among the topics dealt with in a most brief and yet understandable fashion. This book would be worth translating.

This *Medical Report for the year 1926 of the Glasgow Royal Maternity and Women's Hospital*¹⁶ is the first formal report issued by this hospital. Within its walls 3650 cases were treated during the year, with 92 maternal deaths. The entire report is in the form of short, comprehensive tables dealing with every phase of obstetric activities. In addition, 3594 cases were attended in their homes, with only one maternal death.

The Toxemias of Pregnancy, Clinical and Biochemical Study by Cruickshank, Hewitt and Couper, is issued under the aegis of the Medical Research Council of 1927.¹⁷ It is based on 200 cases of toxemia of the second half of pregnancy, and 42 normal pregnant women. This report like the preceding also comes from the Glasgow Royal Maternity Hospital. The material is divided into albuminurias, pre-eclamptic toxemias, nephritic toxemias, and eclampsias. This short monograph goes into a very detailed analysis and has elaborate charts in which all the symptoms are discussed in detail. Careful examinations of the blood and urine are likewise reported. No evidence favoring either an endocrine or parasitic origin of toxemia has been found. A number of possible sources for the toxic factor must be considered including the fetus, placenta, and disturbances of maternal metabolism. The monograph concludes with a careful analysis of the cases in the form of case histories.

Childbirth by the late Dr. William George Lee, of Chicago,¹⁸ is a short, handsomely gotten up book. There is a philosophic introduction, and throughout, the subject is rather discursively and generally presented with few but excellent line drawings as illustrations. The method of treatment, which is almost that of an essayist, makes the reading of this volume easy but leaves the reader with somewhat hazy ideas. Its perusal should be of particular interest to well-instructed laymen or to the medical students just beginning their obstetric work.

¹⁵*Soziale Geburtshilfe und Gynaekologie.* Von L. Fraenkel. Urban & Schwarzenberg, Berlin, 1928.

¹⁶*Medical Report for the year 1926. Glasgow Royal Maternity and Women's Hospital* J. N. Cruickshank, M.D. William Hodge & Co., Ltd., Glasgow and Edinburgh, 1927.

¹⁷*The Toxemias of Pregnancy.* A Clinical and Biochemical Study, by J. N. Cruickshank, J. Hewitt and K. L. Couper. His Majesty's Stationery Office, London, 1927.

¹⁸*Childbirth.* By Wm. G. Lee. The University of Chicago Press, Chicago, 1928.

Miltner has undertaken the sixteenth edition of B. S. Schultze's *Textbook of Midwifery*,¹⁹ the book being designed for midwives rather than for physicians. The first edition of this classic appeared in 1860, the fifteenth edition in 1914. Döderlein has written the introduction. The expansion of the volume is warranted by the fact that in Bavaria the course for midwives has been extended from five to twelve months. The text is clear, concise, and well arranged. Would that our midwives were subjected to a similar intensive course of training.

Burekhard,²⁰ under the guise of an *Obstetric and Gynecologic Therapeutics*, has produced an alphabetically arranged list of German chemical products, interspersed here and there with descriptions of diseases and interventions. The descriptions of diseases and methods of treatment are far from being poor but the drug list resembles that put out by the ordinary pharmaceutical advertiser.

Hammond's *Physiology of Reproduction in the Cow*²¹ was written in 1922 but a short addendum brings the literature up to date. The studies were undertaken mainly to settle practical breeding questions and for milk improvement, but the observations are so accurate that they are important to the physiologist and medical man. In order to test the actual time and duration of estrus, he adopted the method of Ancel and Bouin of using a vasectomized bull. Observations were made on heat, impregnation, the cycle, pregnancy, changes in the udder, and sterility. The study may be considered a valuable *morphologic* contribution and the literature contained is also of use. The latest physiology is not incorporated in the text or in the addendum.

SURGERY AND PUBLIC HEALTH

The third edition of Horsley's *Operative Surgery*²² is a very well-balanced, instructive textbook, covering all phases of surgery adequately, but particularly interesting along certain lines which the author has always emphasized. Chief among these are the biologic versus the mechanic phases of surgery. After all, this point of view will prevent a surgeon from recklessly following fads which have an entirely wrong theoretic basis of which I may instance the metal bone plates so popular a few years ago. Among the numerous newer surgical advances treated of in the book, are a chapter on cicatricial contractions, the Blair-Bell lead treatment of cancer, the numerous new technics for gastric resection, intestinal anastomosis without clamps, Cutlers' operation on the heart, and Sauerbruch's thoracoplasty. Such a purely cosmetic operation as face lifting, is discussed in considerable detail. Only a very short description of peri-arterial sympathectomy is given. Many new and excellent illustrations have been added to the book which will be found most useful for both the student and the practicing surgeon because not only are the elements and general principles given, but Dr. Horsley's many technical innovations are embodied in the text.

Volume VII of the *Medical Department of the United States Army in the World War*²³ has been edited by Col. William N. Bispham, M.C.

¹⁹*Lehrbuch der Hebammenkunst.* Von B. S. Schultze. 16 Auflage. Neu bearbeitet von Dr. v. Miltner. Wilhelm Engelmann, Leipzig, 1928.

²⁰*Geburtschilfliche und gynäkologische Therapie.* Von Dr. Georg Burekhard. Urban & Schwarzenberg, Berlin, 1928.

²¹*The Physiology of Reproduction in the Cow.* By J. Hammond. The University Press, Cambridge, 1927.

²²*Operative Surgery.* By J. S. Horsley. Ed. 3. C. V. Mosby Co., St. Louis, 1928.

²³*The Medical Department of the United States Army in the World War. Vol. VII. Training.* By Col. Wm. N. Bispham. Prepared under the direction of Maj. Gen. M. W. Ireland. U. S. Government Printing Office, Washington, 1927.

It deals with the training of medical, dental, sanitary, and veterinary officers as well as the nurses and medical corps, both in the United States and in the A.E.F.

The various medical officers' training camps, the training in posts, mobilization, and other camps, are taken up in detail. Over 150 pages are devoted to Camp Greenleaf, Georgia, with many illustrations. In summary Fort Riley, Fort Benjamin Harrison, Fort Des Moines are referred to. The special schools, including the Army Medical School, Washington, are discussed. In the army medical school routine medico-military education had been given with attention to hygiene, laboratory work, x-ray, orthopedics and research. Suddenly these activities had to be tremendously expanded. This was done by the aid of professional schools opened at various institutions and universities, of which I instance merely a few such as Yale, Cornell, Washington, Harvard, University Hospital Philadelphia, Rockefeller Institute, New York, etc., etc. A school of nursing is likewise described, as well as the activities necessary to drill and teach dentists, veterinarians and sanitary units.

In the A.E.F. the Army Sanitary School of Longres is described. An appendix of over 500 pages is an *omnium gatherum* which includes subjects from ambrine to x-ray. This volume of the series, of which others have been reviewed, makes interesting reading, is informative and will prove of use in keeping the medical corps active and alive.

Volume IX is a composite description of the communicable and other diseases²⁴ occurring during the World War, in the American Army, both in this country and abroad. A number of authors have described the various phases. Typhoid fever, which in the Spanish American War attacked 114 out of every 1000, in the World War afflicted our army only 0.37 to the 1000. Influenza, on the other hand, caused a tremendous morbidity rate. It was impossible always to differentiate influenza, bronchitis, broncho- and lobar-pneumonia, to which may be credited 80 per cent of the total deaths from diseases occurring during the war.

Volume XIII deals with the important subject of physical reconstruction and vocation by Major A. G. Crane,²⁵ the second and smaller portion of the volume being devoted to the Army Nurse Corps. A voluminous appendix concludes this thick tome.

The report by Cadenat and Patel on *Drainage in Abdominal Surgery*²⁶ was made to the 36th French Surgical Congress. The analysts favor no drainage where the lesion can be eradicated and the peritoneum left or restored to intact condition. They advocate drainage in bad pelvic cases, drainage down to the gall bladder stump, and to the stump of a perforated appendix in which the region cannot be entirely peritonealized, and in regions necessitating anastomosis of the descending colon.

²⁴The Medical Department of the United States Army in the World War. Vol. IX. Communicable and Other Diseases. By Lieut. Col. J. F. Siler. Prepared under the direction of Maj. Gen. M. W. Ireland. U. S. Government Printing Office, Washington, 1927.

²⁵The Medical Department of the United States Army in the World War. Vol. XIII. Part I. Physical Reconstruction and Vocational Education. By Maj. A. G. Crane. Part II, The Army Nurse Corps. By J. C. Stimson.

²⁶Le Drainage en Chirurgie Abdominale. By F. M. Cadenat and M. Patel. Gaston Doin & Cie, Paris, 1928.

The Annual Report of the Surgeon General of the United States for 1927,²⁷ as usual, contains a wealth of information, but does not lend itself to review. Such diverse subjects as the incidence rate for colds, leprosy investigations, malaria, and nutritional diseases will be found in successive paragraphs.

Another important federal report is the Eleventh Annual Report containing the birth, stillbirth and infant mortality statistics for 1925.²⁸

The eighth series of *Methods and Problems of Medical Education* issued by the Rockefeller Foundation²⁹ is about equally divided between European and American Institutions. The internal medical clinics of France, Germany, England, Holland, Canada, and the United States are discussed. Besides that, there are descriptions of surgical clinics in various countries. Heart clinics are also described, and the new obstetric hospital and residents' quarters, University College Hospital, London, is reported. Teaching gynecology, University and Bellevue Hospital Medical School, New York, is included in this volume which contains short descriptions of these various departments.

INTERNAL SECRETIONS AND BIOLOGY

The fourth installment of the third volume of the *Handbuch der Inneren Sekretion* by Hirsch³⁰ contains the completion of Eggenberger's Thyroid, Goiter and Cretinism. Of the 4,000,000 Swiss inhabitants, 30,000 have had goiter operations, but with the expansion of prophylactic measures, this average is rapidly diminishing. A full description of cretinism is given.

Peritz discusses the parathyroid. Without too close scrutiny, he places a number of diseases under the heading of constitutional spasmodophilia and angiospastic dystrophy. He emphasizes nervous hyperirritability and attempts to illustrate a characteristic mouth, and especially discusses cold hands and feet. The theories and therapy of tetany are fully discussed. He is evidently not able to utilize Collip's parathormone because it is not obtainable abroad.

Leschke deals with the diseases of the vegetative nervous system in a most interesting and instructive fashion, giving the applicability of this research to every phase of endocrine disturbance. He goes with great thoroughness into all the reactions, both drug and others, for the determination of changes in the vegetative system, and gives a detailed description of methods of examination, types encountered, etc. Among the diseases dealt with are diabetes insipidus and mellitus, edema, dystrophies, both accompanied by adiposity and atrophy of fat, sleeplessness and sleeping diseases, chorea and myopathies. The installment concludes with a description by Cimbal of psychoses and neuroses from the endocrine aspect. This series is proving to be extremely important and authoritative.

²⁷Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1927. United States Government Printing Office, Washington, 1927.

²⁸Birth, Stillbirth, and Infant Mortality Statistics for the Birth Registration Area of the United States, 1925. Eleventh Annual Report. Part I. United States Government Printing Office, Washington, 1927.

²⁹Methods and Problems of Medical Education (Eighth Series) Division of Medical Education. The Rockefeller Foundation, New York, 1927.

³⁰Handbuch der Inneren Sekretion. Dr. Max Hirsch. III Band, Lieferung 4. Curt Kabitzsch, Leipzig.

Hogben's *Comparative Physiology of Internal Secretion*³¹ is an excellent, well written, extremely conservative, and most judicial presentation. He has confined his discussion to certain phases of the subject and treated these thoroughly without prejudgment. In discussing adrenalin and neuromuscular coordination, he has entirely thrown overboard the tonus theory. On the other hand, he appears to accord considerable value to the effect of the pituitary posterior lobe secretion on vasomotor regulation. The chapter on the ductless glands in the developmental process is extremely interesting. Emphasis is placed on the possible fallacies in the interpretation of metamorphosis as affected by glandular feeding.

Somewhat to my surprise, Hogben appears to accept the tenuous hypothesis of Dixon and Marshall on the effect of ovarian secretion in promoting posterior pituitary secretion which, in turn, is supposed to have a specific excitatory action on the uterus. According to this hypothesis, the case in which I was forced to remove the last remaining ovary during the fifth month of gestation should have gone far overtime if spontaneous labor were to occur at all. Instead of this, the patient had a normal, uncomplicated labor, setting in exactly on the predicted date.

It is rather impossible to agree with Hogben when he quotes and accepts the statement of Geoffrey Smith that the secretion of the ovary or of the testis is not an established fact. Hogben should keep in mind that Loewe and I simultaneously demonstrated by specific methods the presence of the ovarian secretion in the circulating blood.

The Rate of Living by Raymond Pearl³² embodies the expanded lectures given at University College, London, during 1927. The author says that biostatistics is the sign, symbol, and indeed in some respects, the very essence of a separate science, the biology of groups. The volume is based on eight years of study of a carefully controlled life of the fruit fly (*Drosophila melanogaster*). The author deals with mortality in the main, but in order to make the reader understand, he enters into the technic and then discusses density, duration and inheritance of longevity. The rate of life depends on the rate of living. This very readable exposition of a rather difficult subject is well worth while.

Crew, in his *Genetics of Sexuality in Animals*,³³ handles an extremely difficult subject. As he says, until now this subject has dealt mainly with "the significance of ratios between classes of related individuals which appear in successive generations of an experiment starting with two types that differ from another in respect of one or more heritable characters." Crew likewise says, "I dread lest in my presentation I may chill the interest in my subject that I would awaken in the reader." As far as I am concerned, he came near doing so, because I had to start the reading of this book three times before I could become sufficiently interested to continue its perusal, but was then really repaid for the trouble. Perhaps the fault lies in the fact that genetics has developed a language of its own, a terminology and phraseology as distinct from the medical as that used by a lawyer. In the next

³¹*The Comparative Physiology of Internal Secretion.* By Lancelot T. Hogben, M.A. Macmillan Co., New York, 1927.

³²*The Rate of Living.* By Raymond Pearl. Alfred A. Knopf, 1928.

³³*The Genetics of Sexuality in Animals.* By F. A. E. Crew. The Macmillan Co., New York, 1927.

edition I would suggest a readily accessible glossary to help the reader over these first stumbling blocks.

Sex in the higher animals is usually predetermined at the time of fertilization. The author deals with sex determination, parthenogenesis, sex-linked inheritance. For sex reversal there must be a switchover from one type of metabolism to another. The sex ratio is likewise discussed. The presentation is clearcut, concise, but seems very difficult reading for the average medical man.

In my search for a usable *Zoology* for both myself and medical students, I have come across the one by Kerr of Glasgow, published a number of years ago.³⁴ Its comparatively short compass of nearly 500 pages, in spite of profuse illustrations, its clearcut description of morphology, makes it useful. Any medical man who keeps up with biologic literature is constantly obliged to work up the lower forms which are used in experimental laboratories. For this purpose Kerr's book is very desirable. Lack of space has necessitated the omission of the higher vertebrates. Other volumes readily accessible, can overcome this deficiency. On the whole, I have found the book of great use.

The Requirements in Calcium for Human Beings and Animals by Oscar Loew³⁵ is a short monograph appearing in its fourth edition. Only the lowest algi can do without calcium, which is necessary for the heartbeat, the blood coagulation, and other vital functions. Calcium, contrary to the usually accepted views, is even more important for the soft parts than for the bones. Magnesium in excess is antagonistic to calcium. The requirements of the mother and child for calcium are discussed in detail. The author administers calcium in form of kalzan, a calcium double salt lactate of calcium and sodium. Calcium also plays an important part in animal breeding.

MEDICINE

Pathological Physiology of Internal Diseases represents the third edition of Hewlitt's textbook, revised in memoriam by nine of his colleagues.³⁶ The general form of the previous editions has been more or less kept up. Hewlitt was primarily a physiologist who drifted into medicine and who, therefore, was both desirous and well fitted to bring the clinic and laboratory together. The main object of the book has been and still is, to show the changes in function due to internal diseases. The various systems have been covered seriatim. To the heart and blood vessels 140 pages are devoted. One-half of this space is given to digestion and absorption. Metabolism, both nasal and other, is taken up. Next the diseases of the liver and pancreas are dealt with, followed by disturbances of the kidney, disturbances of heat regulation, fever, with two shorter chapters dealing with the endocrine and nervous diseases. Each chapter is concluded by a good, detailed, working bibliography. The volume is so arranged as to make reference to it quick and easy. A tremendous amount of information is contained within its pages in concise, didactic form.

The twentieth edition of a *Textbook of Practical Therapeutics* by

³⁴*Zoology for Medical Students.* By J. Graham Kerr. Macmillan & Co. Ltd., London, 1921.

³⁵*Der Kalkbedarf von Mensch und Tier.* Zur chemischen Physiologie des Kalkes. Oscar Loew. Ärztliche Rundschau, Otto Gmelin, München, 1927.

³⁶*Pathological Physiology of Internal Diseases. Functional Pathology.* By A. W. Hewlitt. Revised in Memoriam by his Colleagues under the Editorial Supervision of George De Forest Barnett. D. Appleton and Co., New York.

³⁷*A Textbook of Practical Therapeutics.* By Hobart Amory Hare. Ed. 20. Lea & Febiger, Philadelphia, 1927.

Hobart Amory Hare³⁷ has appeared and, like each preceding edition, has been really thoroughly revised and kept up-to-date. Early in my medical career I acquired the habit of looking up prescriptions, short descriptions of diseases, methods of treatment in this epitome, compend and textbook combined, and this habit has persisted, because Hare's treatise is unique for its short, clear, and specific instructions and descriptions. Probably some of its usefulness is due to the fact that the author has never hesitated to obtain the collaboration of leaders in special topics. In this edition this applies particularly to the eye, to the treatment of puerperal diseases and abortion, transfusion, artificial pneumothorax, diseases of the skin and syphilis. Even such recent topics as the antiscarlatinal and antimeasle serum are discussed. The division into drugs, other remedial measures, feeding, diseases, and very detailed indices has been kept up. I know of no purer mine of information than these more than 1000 pages embody.

Another book by Hobart Amory Hare is the *Use of Symptoms in the Diagnosis of Disease*.³⁸ It has already reached its ninth edition. The aim of this volume is the recognition of symptoms leading to diagnosis, or, conversely, the upbuilding of a diagnosis by grouping of symptoms. This volume likewise is concise, to the point and most instructive. The arrangement is partly regional (as of the face and body), partly symptomatic (as convulsions, coma, pain). An excellent sample of the completeness of this short volume is furnished by the subject of rashes, for example, in which every conceivable etiologic factor is entered into with great detail.

Under the heading, *Collected Studies and Reports, University of Iowa Studies in Medicine*,³⁹ are gathered varia, reprinted from medical journals. Many topics are dealt with, mainly in physiology, cardiology, pharmacology, and neurology. The collection contains 40 articles by numerous authors.

The American Medical Association of Vienna has its own journal called *Ars Medici* of which volume v, number 1 of the year 1927⁴⁰ has been submitted for review. In it will be found a review of some German and Austrian literature which is well arranged, well extracted, but far from complete. It also contains the local Viennese medical notes and gossip. This journal should appeal to the Americans abroad as well as to Americans who have spent time in Vienna and are interested in its local happenings. As a review journal its scope is too small to be inclusive.

MISCELLANEOUS

The fourteenth edition of Delafield and Prudden's *Textbook of Pathology*, revised by Francis Carter Wood⁴¹ appears as a well tried and old friend. Although keeping up the format, arrangement, and general appearance which has endeared it to its readers over so many years, this edition takes cognizance of all the newer developments in pathology, including the keeping of bibliographic references up-to-date. Therefore, the reader will find vitamins and hormones discussed, changes in the description of liver and gall bladder, as well as

³⁷*The Use of Symptoms in the Diagnosis of Disease.* By Hobart Amory Hare. Ed. 9. Lea & Febiger, Philadelphia, 1928.

³⁹*University of Iowa Studies in Medicine.* Collected Studies and Reports. Vol. III. No. 1. The University, Iowa City, Iowa, 1927.

⁴⁰*Ars Medici.* The Journal of the American Medical Ass'n of Vienna. Volume V, Number 1, Vienna, January, 1927.

⁴¹*A Textbook of Pathology.* By F. Delafield and T. M. Prudden. Ed. 14. Revised by F. C. Wood. Wm. Wood & Co., New York, 1927.

the pancreas and lungs. In order not to increase the size of the volume unduly, the editor has deleted the chapter on lesions following poisoning.

The third volume of the *Ergebnisse der medizinischen Strahlenforschung*⁴² has just appeared, covering a huge field as will be seen from this partial résumé of its contents. The roentgen diagnosis of the nose and accessory sinuses (Steurer); of the ears (Steurer); of acoustic tumors (Schüller); of fractures of the petrosal bone (Schüller) deal with the head. Brauer and Lorey cover x-ray of the bronchi by means of contrast media; Teschendorf of the esophagus; Dillon, of unilateral persistent elevation of the diaphragm; Fleischner, tuberculosis of the intestine. Appendicular x-ray is taken by Gottheiner, while d'Amato has gone into the contrast filling of the gall bladder by Graham and Cole's method. Stern treats of lung echinococcus; Schinz and Slotopolsky give a most interesting exposition of the radio biology of the skin with most instructive microscopic pictures of the changes that the skin undergoes. Lippman discusses light and metabolism while Schempp treats of adenoids and nasal pharyngeal polypi. Of particular interest to the gynecologist is the diathermy treatment in gynecology by Schoenholz, who goes into the theory and technic in great detail. Throughout, the lavish and beautiful illustrations mentioned in the previous volumes, are in evidence in this number. The text contains 613 figures.

Under the heading of *Archives Roumaines de Pathologie Expérimentale et de Microbiologie*, a new journal has been ushered in under the direction of J. Cantacuzène.⁴³ Volume I, number 1, of January, 1928, has been submitted for review. The journal is a quarterly. The editor originally studied in the Pasteur Institute for many years and has gathered a group of workers around him in Roumania during the last twenty-five years. The format, typography, and illustrations of this journal are good, verging on the lavish.

The first article by the editor himself, deals with the immunity reactions in invertebrates. The animal used in this investigation is sipunculus nodus. This paper contains 24 gorgeously colored plates.

The next article by Combiesco deals with the study of anthrax infection, the bacteria being placed in capillary tubes in the skin and peritoneum. The organisms rapidly acquire resistance against the tissue juices.

Ciuea and Alexa find that stovarsol cannot replace quinine in the routine treatment of malaria.

Parhon, Marza and Cahane have communicated an elaborate investigation on the water contents of organs and tissues under the influence of the nervous and endocrine system. The central end of a cut nerve, as well as denervated muscle, contains more water than the normal. There are several other articles in this new journal, to which we wish success.

The last number of *International Clinics*⁴⁴ deals mainly with travel clinics, many of which are informative. The radium home at Stockholm is interestingly described. Over 5000 patients a year are treated. The

⁴²*Ergebnisse der medizinischen Strahlenforschung (Roentgendiagnostik, Roentgen-, Radium- und Lichttherapie)*. H. Holfelder, H. Holthausen, O. Jüngling, H. Martius. Band III. Georg Thieme, Leipzig, 1928.

⁴³*Archives Roumaines de Pathologie Expérimentale et de Microbiologie*. Publiées sous la Direction de J. Cantacuzène. Tome I. Masson et Cie, Paris, 1928.

⁴⁴*International Clinics*. Volume IV. Series 37, 1927. J. B. Lippincott Co., Philadelphia, 1927.

home owns 1673 mg. of radium and has 3 deep x-ray apparatuses, using 180 kv. at 6 milliamperes. Since 1910 they have treated 13,500 patients with malignancy. Forssell considers radium and x-ray as a local treatment of carcinoma only.

There are three articles dealing with duodenal ulcer, from Carson of London; Wilkie of Edinburgh; and Paterson of London. Schilling of Oslo discusses pneumoradiography of the kidney.

An interesting article by Oliver of Baltimore illustrates the medicine of the middle ages, with reproduction of illustrations.

Of the numerous contributions to *International Clinics*⁴⁵ I mention in passing, Garberson of Miles City, Montana, who gives a nice résumé of Tularaemia. Colp, of New York, describes pedicle grafts and their manifold applicability in surgery. Dudgeon and Patrick, of London, recommend a rapid diagnostic method which consists in taking a surface scraping of the tumors to be examined and spreading this out evenly on a glass slide. While still wet the spread is immersed in Schaudinn's fluid and then strained with hemalum and eosin, the entire process requiring from eight to ten minutes. Of 231 specimens examined, 9 diagnoses later were proved wrong in paraffin section.

Under the aegis of the Burke Foundation, Bryant has issued a volume on convalescent changes dedicated to the cause of better convalescent care.⁴⁶ This volume aims to be a source book for the guidance of the workers. It has been found that the community requires 10 per cent as a minimum of convalescent beds, based on the number of hospital beds needed.

The author enters into the history of convalescent care, describes in considerable detail the early convalescent aid at Vincennes (Paris) started in 1857. The Burke Foundation began in 1915. In the Cleveland hospitals, it is claimed, 85 per cent of hospital patients require convalescent care. The Houses of Rest in Russia are described; also the convalescent care to be found in the United States Army. Special attention is devoted to surgical convalescence and finally a literature of the subject is offered.

*Baby's Health Day by Day*⁴⁷ in art imitation leather binding, is a daily diary designed for the mother, I should say, rather than for the infant. Glancing at the uniformity of each page, there is some danger that the modern infant must suffer from monotony and standardization. The daily menu of the newborn, according to this booklet, appears to consist of milk, dextro-maltose, orange juice, cod liver oil, cereal, egg yolk, and "other foods." All the other amusement supplied for the baby seems to be outdoors, sleep, bath, temperature, bowel movement, and weight. I wonder how many mothers will keep such a record continually, certainly not the average multipara or mother of twins.

The Cause and Control of Sex in Human Offspring, by R. Clay Jackson,⁴⁸ "bound in beautifully embossed fabrikoid" is a most curious production by a layman who has gathered a tremendous amount of material from various sources, put it together, and has drawn unwarranted conclusions from this material. According to the author, meteorology is the controlling factor. The book is self published.

⁴⁵*International Clinics*. Vol. 1, Series 38, J. B. Lippincott Co., Philadelphia, 1928.
⁴⁶*Convalescence*. Historical and Practical. By J. Bryant. The Sturgis Fund of the Burke Foundation, New York, 1927.

⁴⁷*Baby's Health Day by Day*. Professional Press, Inc., Chicago.

⁴⁸*The Cause and Control of Sex in Human Offspring*. R. Clay Jackson. Allstrum Printing Co., Tacoma, Washington, 1926.

Selected Abstracts

Ovarian Transplantation

Tuffier, Th., and Letulle, Maurice: Transposition of the Ovary with Intact Vascular Pedicle into the Uterus after Ablation of the Tubes (29 operations). La Presse Médicale, Paris, 1924, May 28, p. 465.

This operation has been devised by Tuffier in an attempt to conserve the function of menstruation and the possibility of fecundation in women in whom a double salpingectomy becomes necessary. As a preliminary, the uterus is dilated with laminaria tents, of increasing size, changed every 12 hours, until its whole cavity is large enough to admit the index finger or the thumb. Just before the laparotomy, the last tent is removed and the cavity is disinfected with tr. iodine. At operation, the tubes are removed, hemostasis being secured by ligating two of the three small branches of the ovarian artery which supply the tube; but rather than ligate the outer, or tuboovarian branch, it is better to leave the tubal fringe which is adherent to the ovary. After incising the uterus through the mucous membranë, either longitudinally or transversely, one ovary (or even both ovaries) either whole or reduced in size by resection, is introduced into the incision so that its greater part protrudes into the uterine cavity. The uterine wall is closed around the pedicle, and the pedicle itself fastened to the uterine serosa, care being taken not to constrict the vessels. The abdomen is closed without drainage.

The results have been satisfactory. The patients have menstruated regularly, with premenstrual pain in 20 per cent. There have been no pregnancies in these 29 patients, but Raymond Petit has had one case with delivery of a live child at term, while Estes, in 27 cases, reported 2 full-term living children and 2 miscarriages, at 3 and 4 months. The probability of pregnancy is not great, but the operation makes it possible that a young woman operated upon for double salpingitis might conceive.

In one case, Tuffier found it necessary to perform hysterectomy nine months later on account of intestinal obstruction from adhesions to the uterus on the side opposite to the transplantation. About one-third of the ovary was found protruding into the uterine cavity. The author thinks that this was not quite sufficient; on the other hand, if the whole ovary is in the cavity, it will act as a polyp. This specimen was studied microscopically by Letulle, who reported that the ovary was living and functioning. Many cysts were present, one of them being fairly large, as well as many corpora lutea, "more or less old."

E. L. KING.

Sippel, Paul: Technique of Ovarian Transplantation. Münchener Medizinische Wochenschrift, 1926, lxxiii, 155.

Most previous ovarian homotransplants were intraperitoneal. There have also been devised intratubal (Martin) and adnexal stump transplantations. Extraperitoneal transplantations have been done in the abdominal wall or fascia by Unterberger and Tuffier and also in the vagina by Engel and Glass, and in the right breast by Brewitt. The success of the operation seems to be largely a ques-

tion of sufficient blood supply, insuring subsequent nutrition for renewed growth. Muscle or mesentery, therefore, seems particularly favorable from this standpoint.

Auto- and homotransplants have been made in the muscular and fascial layers. When these are done, the ovary must be transferred while still warm; in homotransplants the ovaries are transplanted immediately. In autotransplants the grafted ovaries are not carried over until the abdomen is ready to be closed. In one case the ovary and blood vessels were transplanted into the right rectus muscle. The grafted ovary healed perfectly and menstrual changes occurred regularly.

The difference in the subsequent clinical course between the intra- and extra-peritoneal operation is not clearly defined. In homotransplants various types of growths develop which finally hinder ripening of the follicles. Likewise cystic degenerative changes occur in autotransplants.

W. B. SERBIN.

Herschman, O.: Intrauterine Implantation of the Ovary with Preservation of the Ovarian Circulation. *Klinische Wochenschrift*, 1927, vi, 114.

The author reports two cases in which, following salpingectomy, the ovary together with its intact circulation was transplanted into the uterine cavity. In both cases normal menstruation was established following the operations. Neither case had been followed by pregnancy at the time of the report but Herschman does not see why this cannot occur. He recommends this procedure in all cases of bilateral salpingectomy where further pregnancies are desired. The method can even be used following a defundation. The implanted ovary does not act as a foreign body and there is apparently no danger of setting up an intrauterine infection or inflammation.

RALPH A. REIS.

Petinari, V.: Ovarian Grafts and Their Application to Therapy in the Human. *Gynécologie et Obstétrique*, 1926, xiii, 19.

The following conclusions are based on experiments made on 332 animals of different species. Ovarian tissue can be made to live and to continue the elaboration of the normal internal secretion, and even the germinal function, where the grafted tissue is from the same species as the receptor. The formation of corpora lutea is seen chiefly in the autoplasmic grafts, whereas, in the heteroplasmic grafts, follicle atresia is the rule.

Ovarian secretion which cannot be replaced by any of the other internal secretions can be resupplied to the needy organism by successfully grafted ovarian tissue. In this way, a whole series of disorders dependent upon the disordered endocrine function may be remedied.

For a graft to take, it is necessary for the organism to show an absolute or relative lack of the sexual hormone. A long period of castration, the absence of the uterus, or both, reduce the probability of a take. The physiologic effect is apt to be spasmodic, and to simulate rather than duplicate the normal function. At times, it may exaggerate it. A successful graft will prevent the appearance of the usual effects of castration, will carry the organism to its usual sexual development, and has on old animals a definite general specific action, causing a profound psychic and somatic change. Much of the work done to date lacks scientific value. Neither extreme optimism nor pessimism is justified.

The following syndromes may be favorably affected by ovarian graft: (1) Infantism; (2) Castration with pathologic menopause; (3) Dysovarium, with ovarian insufficiency; (4) Ovarian sterility; (5) Pluriglandular endocrine syndromes; (6) Certain mental affections.

In the human, autoplasmic transplants give the best prognosis. Homoplasmic

grafts have occasionally been satisfactory. The tissue may be grafted into the genital organs themselves (uterus, tubes) or into tissue in the region of the genitals or even into other tissues at some distance from the pelvis. Grafts may be used to stimulate impotent ovarian tissue as well as to replace removed or destroyed tissue. Transplantation from chimpanzee to human has been tried and evokes interesting speculation. Ovarian grafts have great therapeutic possibilities and their use will become more general in the treatment of conditions not amenable to other ovarian therapy. At present they are to be used with discretion.

GOODRICH C. SCHAUFFLER.

Pankow, O.: Ovarian Transplantation in Humans. *Therapie der Gegenwart*, 1926, lxvii, 68.

The author transplants a piece of ovarian tissue into a place between the bladder and cervix or into the rectus muscle of the abdomen. In the latter instance he cuts a window in the fascia over the transplant to prevent pressure on it. He has removed such a transplant three and one-half years later and found primordial and ripening follicles.

Menstruation occurs in from 2 to 6 months and has continued for 8 years. The younger the patients the longer menstruation keeps up. If it does not occur in 6 months it will not appear.

Homotransplantation is used in patients who have been castrated; those who have an extreme degree of hypoplasia; and those who have hypofunction of the ovarian secretory apparatus. It is most beneficial in the last class. These patients menstruate at long intervals and if treatment with thyroid, ovarian and pituitary extract among other means does no good the transplantation may be tried. The longer the symptoms have continued and, especially the longer the time after castration, the less chance there is of obtaining a beneficial result.

Lately homotransplantation has been employed in dementia precox with some improvement because such patients frequently have hypoplasia of the genital organs. Sippel has used it in menorrhagia at puberty and at the climacteric on the theory that the corpus luteum does not form and the follicle persists causing the bleeding. He believes that introducing normally functioning ovarian tissue stimulates the patient's ovaries.

FRANK A. PEMBERTON.

Loeser, A.: The Action of Ovarian Transplantation upon Infantile, Endocrine-Deficient, and Old Women. *Medizinische Klinik*, 1926, xxii, 1637.

The author reports his experiences with ovarian transplantation during the past five years. The operation itself is absolutely harmless but good material is hard to obtain. The author did not use the ovaries from patients with cancer or pulmonary tuberculosis, nor did he use ovaries preserved on ice. He obtained functioning ovaries from patients on whom he performed myomectomy or suspension operations. A transplanted ovary must be imbedded in a place where there is active metabolism such as muscle, not fat.

The author performed 16 transplantation operations. There were 4 infantile women, 5 amenorrhoeic women who had many disturbances of internal secretion, and 7 women with menopausal symptoms after operative castration or premature menopause. In the infantile patients, there were no good results; neither were the results good in the amenorrhoeic women with internal secretory disturbances. However, in the patients who had previously experienced normal ovarian activity and who lost it by operation, transplantation produced a definite beneficial effect.

In these patients the transplanted ovary was not placed in a constitutionally sick but in a normal individual. The viability of the transplant is short, for in no case did the effect last more than a year and one-half.

In two cases, ovaries from children were transplanted and both yielded good results.

J. P. GREENHILL.

Sippel, Paul: The Homoplastic Transplantation of Ovaries in Schizophrenia.
Klinische Wochenschrift, 1925, iv, 401.

After the satisfactory results obtained by homoplastic transplantation of ovaries in primary and secondary hypogenitalism he enlarged the field of transplantation to schizophrenia. In schizophrenia (dementia precox) a considerable percentage of cases have a more or less pronounced hypoplasia and underfunction of the genital system. In a series of 176 such cases Fraenkel has found that 72 per cent showed infantile changes of the genitals in a severe form. Geller has concluded, with Mott, Fraenkel, Hauck, and Koehler, that there is a close relationship between subnormal genital function and dementia precox.

On the basis of these findings and his own researches, Sippel has to date transplanted ovaries to six young schizophrenic women. A close control of their psychiatric conditions was possible as these cases were kept in the Hospital for Mental Diseases at Dalldorf.

The operated cases were between eighteen and twenty-four years old. The majority showed a marked malnutrition and definite underdevelopment. The status of the genital system was definitely ascertained by means of diagnostic curettage and laparotomy, and revealed mild, medium, and severe grades of hypoplasia. In five cases the endometrium was entirely functionless. In three cases there was a mature ovum in the ovary and no corpus luteum formation. In two cases an old corpus luteum in advanced retrogression was found, which did not fit in with the stated menstrual period. In practically all cases there was pronounced disturbance of maturation of the ovum associated with a functional disturbance of the uterine mucosa due to hypoplasia.

Two girls, showing early schizophrenia with a light grade of hypogenitalism, showed progressive improvement two to four weeks after transplantation. Their hallucinations, negativism, and depressive symptoms disappeared almost entirely, their periods were more normal, they took on a healthy appearance and were discharged as improved two months after transplantation.

In one case, aged nineteen, with schizophrenia of two years duration and marked underdevelopment of the genital system, the psychiatric condition was unchanged after operation.

The author will report follow-up observations of these cases at a later date.

C. A. SAFFERT.

Correspondence

The Baldwin Operation for the Formation of an Artificial Vagina

To the Editor.—Since the original publication of the method which I had devised for the making of a vagina in cases of congenital or acquired absence of that viscus (*Annals of Surgery*, September, 1904), a good deal has been written in regard to the operation, and relatively a large number of operations have been performed. The reports of deaths, particularly those in the work of foreign operators, have been most distressing to me because it had seemed to me that the operation properly performed should have a low mortality. Some of this mortality has apparently been due to unwise deviations from the original technic, and some perhaps to misunderstanding from lack of familiarity of the surgeons with the language in which my report appeared.

In my original description of the operation and in all my subsequent writings I advised the use of the lower end of the ileum for the formation of the vagina. I had previously examined the mesentery in many hundreds of cases, in connection with abdominal operations, and had always found it ample for the purpose in mind, and in my subsequent operations I have had no trouble in using that portion of the bowel. Because, however, of the possibility of a short mesentery I suggested the use of the sigmoid in case such shortness would preclude the use of the ileum.

The length of bowel to be utilized should be no more than enough to make a normal vagina. With that amount I have never had any complaint of any leucorrheal discharge, and in examining such patients later have never found more than the normal amount of moisture present. A Russian surgeon some time ago reported a series of cases which he had had in which there was present an annoying leucorrhea, but the x-ray pictures which accompanied his report showed that he had used an enormous excess of ileum.

The opening for the vagina should be made by a transverse incision at the proper point in the perineum. The line of cleavage would be found so that the separation of the bladder and the rectum could be made rapidly and safely. (In one case I had a good deal of difficulty in making this separation because a previous operator had attempted to construct a vagina by making an opening and packing it with gauze, expecting nature to cover the raw surface with mucous membrane. I found a mass of scar tissue, but was able to work through it without injury to bladder or rectum.)

In selecting the piece of bowel to be utilized its mesentery should be studied so as to be sure that the blood supply to that part of bowel is ample. The ends of the resected bowel should be closed by a purse string with inversion as usual, and the continuity of bowel should be restored either by lateral anastomosis or Murphy button; but care should be taken to so close the opening in the mesentery as to obviate postoperative ileus.

By means of a hemostat pushed through the mesentery at the center of the resected portion a strip of gauze is pulled through to be used for traction in bringing the bowel down through the new passage. After the loop of bowel is in place the floor of the pelvis should be carefully examined to see that all raw surfaces are covered over.

After completing the perineal work, as described in my original article, care should be taken to pack a sufficient amount of gauze in each half of the bowels so as to keep its peritoneal surface in snug contact with the raw surface of the new canal.

As stated in all of my communications on this subject, the operation is distinctly not one for a surgical tyro, but it is an operation which can be made by an expert without difficulty and with no more danger than would attend an ordinary operation requiring intestinal resection. The making of the new opening should certainly give no shock or hemorrhage. (In my own work I have had but one death, and that I am confident would not have occurred had the patient and her husband been intelligent enough to cooperate; but they were foreigners and would not allow stomach lavage or enemas and the patient died, but with no evidence of peritonitis. No postmortem was permitted.)

I have never been able to understand the statements of certain writers as to the alleged high mortality of the operation. The statistics, as far as I have seen them, have all been foreign and out of all proportion to those furnished to me personally by American surgeons. A satisfactory explanation of this mortality is afforded, however, by an abstract from the *Press Medicale*, in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* for May, 1928, page 734. In this abstract reference is made to ninety cases which had been collected with a mortality of 17 per cent. These fifteen fatalities were due to peritonitis in twelve cases, and in nine of these the peritonitis was due to intestinal gangrene! This report clearly solves the mystery of the mortality reported by these European surgeons. They certainly cannot be familiar with good surgical technic, or even with the principles of ordinary asepsis, to have such a number of deaths from peritonitis; particularly when so much of that peritonitis was due to failure to look after the blood supply to the loop of the bowel.

I may add that the method of operating which I originally described I have found entirely satisfactory. Several surgeons have suggested changes, but not one of those suggestions seemed to me to be any improvement, and several were decidedly objectionable. Incidentally I may state that within a few weeks the husband of my first patient, operated upon 21 years ago (*American Journal of Obstetrics and Diseases of Women and Children*, November, 1907), happened to come to the city from his distant home and called on me to report that his wife was still well and everything in every way normal. Her operation was necessitated by the complete loss of her vagina by sloughing following childbirth.

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Menstruation and Pseudomenstruation

To the Editor.—The article by Professor Corner which appeared in the *Journal of the American Medical Association* (Nov. 26, 1927, lxxxix, 1838) has interested me greatly. In it the author describes two processes which occur in the female macacus rhesus, both accompanied by the same clinic symptoms; namely, periodically recurring bleeding from the vagina. The genesis of these two vaginal bleedings are evidently fundamentally different. In the one case, we are dealing with bleeding from a surface wound due to destruction following a specific endometrial change; in the second case we are evidently dealing with a hemorrhage due to diapedesis through a resting mucosa. It appears essential, therefore, to distinguish and give different names to these quite distinct processes. Unless this is done, confusion will arise in the study of the etiology. The same would apply to the confusion arising in clinic investigation if these two quite distinct processes

were regarded from the same point of view. As will be evident from my monograph, as well as the work of Robert Meyer and others, the cyclical process, together with the destruction of the mucosa, must be regarded as a consequence of the failure of impregnation and therefore as an important functional complex which deserves separate recognition and separate nomenclature. Menstruation, throughout the ages, has popularly been regarded as closely associated with pregnancy. It appears to be both necessary and logical to confine the term "menstruation" to the breaking down of the pregravid uterine mucous membrane. The hemorrhage which Corner describes, requires to be put under a different heading, as "menstruation-like bleeding," or "pseudomenstruation," the discovery of which in monkeys living under the artificial conditions of cage life are of extreme interest, particularly as they appear at relatively cyclical intervals. For a moment we are unable to explain these phenomena. Possibly one will find by means of systematic quantitative examinations for the female sex hormone in the blood of these animals that certain cyclical ripening processes may occur in their germplasm at puberty even before full physiologic ability to become impregnated has been reached and before ovulation actually takes place.

Clinically, a great number of nonmenstrual hemorrhages are known, of which in the second portion of my monograph I have given many examples. However, no identical, fully rhythmical types, such as Corner describes in the monkey, have yet been found in the human being. It will therefore be necessary to direct attention and research in human cases to see whether in them likewise cyclical recurrence of pseudomenstruations can be found. Up to date all such data are wanting in the human being. It would be of extreme value to submit the genitals of those monkeys which show the anomaly in question to an exact analysis of their germplasm function, and also to determine the number of follicles, the various stages in which found, and the exact morphology of the endometrium. Dr. Corner's valuable contribution will be enhanced if he does not designate these two types of genital bleeding with the name of "menstruation," reserving the term of "menstruation" for the final stage of an abortive pregnancy and calling the genetically different bleeding from the genitals by the name of "pseudomenstruation." Unless this is observed there is danger that the beginning clarification of our concept of menstruation will again be obscured.

(Signed) DR. ROBERT SCHROEDER, Professor, Director der
Universitäts-Frauenklinik in Kiel.

Books Received

ERGEBNISSE DER MEDIZINISCHEN STRAHLENFORSCHUNG (Roentgen-diagnostik, Roentgen-, Radium- und Lichttherapie). Band III. Mit 613 Abbildungen im Text. Verlag von Georg Thieme, Leipzig, 1928.

CHILDBIRTH. By William George Lee, A.B., M.D. The University Press of Chicago, 1928.

INTERNATIONAL CLINICS. Volume I. Thirty-eighth Series, 1928. J. B. Lippincott Company, Philadelphia, 1928.

THE USE OF SYMPTOMS IN THE DIAGNOSIS OF DISEASE. By Hobart Amory Hare, professor of therapeutics and diagnosis in the Jefferson Medical College of Philadelphia, etc., etc. Ninth edition, thoroughly revised. Illustrated with 124 engravings and 4 plates. Lea and Febiger, Philadelphia, 1928.

THE RATE OF LIVING. Some experimental studies on the biology of life duration. By Raymond Pearl, Johns Hopkins University. Alfred A. Knopf, New York, 1928.